IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

Mitsubishi Tanabe Pharma Corporation
2-6-18, Kitahama, Chuo-ku, Osaka-shi,
Osaka 541-8505, Japan

Plaintiff,

v.

Civil Action No. _____

HON. David J. Kappos
Under Secretary of Commerce for Intellectual
Property and Director of the United States
Patent and Trademark Office
Madison Building
600 Dulany Street
Alexandria, Virginia 22314

COMPLAINT

Plaintiff Mitsubishi Tanabe Pharma Corporation for its complaint against Defendant the Honorable David J. Kappos, state as follows:

1. This is an action by the owner of United States Patent No. 7,566,728 ("the '728 Patent") seeking review of inaccurate and erroneous Patent Term Adjustment ("PTA") calculations made by the United States Patent & Trademark Office ("USPTO"). Specifically, this is an action by Plaintiffs under 35 U.S.C. § 154(b)(4)(A) seeking a judgment that the patent term adjustment of 544 days calculated by the USPTO for the '728 Patent should be corrected to 1145 days.

2. This action arises under 35 U.S.C. § 154 and the Administrative Procedure Act, 5 U.S.C. §§ 701-706.

I. THE PARTIES

3. Plaintiff Mitsubishi Tanabe Pharma Corporation is a company operating under the laws of Japan. Mitsubishi Tanabe Pharma Corporation is incorporated at 2-6-18, Kitahama, Chuo-ku, Osaka-shi, Osaka 541-8505.

4. Defendant David J. Kappos is the Under Secretary of Commerce for Intellectual Property and Director of the United States Patent and Trademark Office. Defendant is sued in his official capacity.

II. JURISDICTION AND VENUE

5. This Court has jurisdiction over this action and is authorized to issue the requested relief to Plaintiff pursuant to 28 U.S.C. §§ 1331, 1338(a) and 1361; 35 U.S.C. § 154(b)(4)(A) and 5 U.S.C. §§ 701-706.

6. Venue is proper in this district pursuant to 35 U.S.C. § 154(b)(4)(A).

7. This Complaint is being timely filed in accordance with 35 U.S.C. § 154(b)(4)(A).

III. BACKGROUND

8. The inventors of the '728 Patent are Koji TESHIMA and Masanori MINOGUCHI.

9. The '728 Patent granted on July 28, 2009, based on U.S. Patent Application No. 10/508,339, which is a U.S. national stage of International Application PCT/JP03/03925 filed March 28, 2003. The International Application

PCT/JP03/03925 claimed foreign priority of Japanese Application No. 2002-093398 filed on March 29, 2002. The '728 Patent is attached hereto as Exhibit A.

10. Plaintiff Mitsubishi Tanabe Pharma Corporation is the Assignee of the '728 Patent, as evidenced by the Assignment recorded in the USPTO at Reel/Frame 015938/0836 and the Change of Name recorded in the USPTO at Reel/Frame 020838/0701, and is the real party in interest in this case.

11. When the USPTO issued the '728 Patent on July 28, 2009, it erroneously calculated the entitled PTA for the '728 Patent as 544 days. Had the USPTO calculated the entitled PTA properly, the '728 Patent would be entitled to 1145 days of PTA.

12. The errors in the USPTO's PTA method of calculation are detailed a decision from the U.S. District Court for the District of Columbia where the Court granted summary judgment against the USPTO, holding that the USPTO's PTA calculation methodology was erroneous as a matter of law and inconsistent with the Patent Statute, *see Wyeth v. Dudas, 580 F. Supp. 2d 138 (D.D.C. 2008).* The *Wyeth v. Dudas* opinion is attached as Exhibit B. This decision was appealed to the United States Court of Appeals for the Federal Circuit, which, on January 7, 2010, handed down a decision that the USPTO has been calculating PTA incorrectly in certain circumstances, ultimately affirming the District Court's original decision, *see Wyeth v. Kappos, No. 09-1120 (Fed Cir. Jan 7, 2010).* The *Wyeth v. Kappos* decision is attached as Exhibit C.

13. The correct PTA methodology identified in the prior *Wyeth v. Dudas* action governs the USPTO's calculation of PTA for Plaintiff's '728 Patent.

IV. COUNT I: U.S. PATENT NO. 7,566,728

14. Plaintiff incorporates by reference the allegations in paragraphs 1-13 above, as if fully set forth herein.

15. During prosecution of the '728 Patent, the patent owner of the '728 Patent accrued 575 days of PTA under 35 USC § 154(b)(1)(A), and accrued an additional 570 days (= 668 days of USPTO's delay – 98 days of Applicant's delay) of PTA under 35 USC 154(b)(1)(B).

16. Under the USPTO's interpretation of 35 USC § 154, all PTA accrued under 35 U.S.C. § 154(b)(l)(A) and all PTA accrued under 35 USC § 154(b)(l)(B) inherently overlap and, thus, it has been the USPTO position that a patent holder is only eligible for the larger of these two amounts of PTA. In addition, the USPTO erroneously calculated the USPTO's delay under 35 USC § 154(b)(l)(B) as 642 days (see paragraph 20, below), and therefore erroneously limited the PTA for the '728 Patent to 544 days (= 642 days – 98 days of Applicant's delay) as shown on the face of the '728 Patent.

17. In view of *Wyeth v. Dudas*, all days on which 35 USC 154(b)(1)(A) or 35 USC 154(b)(1)(B) apply should accrue PTA for the '728 Patent.

18. Under *Wyeth v. Dudas*, each day from the day after December 25, 2005 (fourteen (14) months from the date on which the International application fulfilled the

requirement of 35 U.S.C. § 371 (i.e., § 371(c) Date October 25, 2004)) through to the grant date on July 28, 2009, qualifies for PTA under 35 U.S.C. § 154(b)(1)(A) (575 days), and each day from the day after September 29, 2007 (three (3) years from the "actual filing date" under 35 U.S.C. § 154(b)(1)(B)) through to the grant date on July 28, 2009, qualifies for PTA under 35 U.S.C. § 154(b)(1)(B) (668 days).

19. **USPTO's Delay under 35 U.S.C. § 154(b)(1)(A)**

Plaintiff concedes that the total USPTO prosecution delay under 35 U.S.C. § 154(b)(1)(A) is 575 days due to the USPTO's failure to issue an Office Action within fourteen (14) months after the date on which the international application fulfilled the requirements of 35 U.S.C. § 371, as the USPTO originally calculated. In particular, this 575-day delay is calculated from December 25, 2005 (fourteen (14) months after the date on which an international application fulfilled the requirement of 35 U.S.C. § 371 (i.e., § 371(c) Date of 10/25/2004)) through to July 23, 2007 (the date of the first Office Action).

20. **USPTO's Delay under 35 U.S.C. § 154(b)(1)(B)**

In calculating the USPTO prosecution delay accrued under 35 U.S.C. § 154 (b)(1)(B), Plaintiff disagrees with the USPTO's holding of a total USPTO prosecution delay of 642 days under 35 U.S.C. § 154(b)(1)(B) because this delay is erroneously calculated from October 25, 2007 (the day that is three years from the § 371(c) Date of October 25, 2004)) through to the grant date on July 28, 2009. Plaintiff contends that this delay should have been calculated from

September 29, 2007 (the day that is three years from the "actual filing date" of the '728 Patent (September 29, 2004)) through to the grant date on July 28, 2009.

In particular, since the '728 Patent was granted from a U.S. national stage application filed under 35 U.S.C. § 371, according to 35 U.S.C. § 154(b)(1)(B), 37 C.F.R. § 1.702(b), 35 U.S.C. §§ 371(b) and (f) and Article 22 (1) or (2) or 39 (1)(a) of the Patent Cooperation Treaty, the "actual filing date" of the '728 Patent, for the purpose of calculating the USPTO prosecution delay under 35 U.S.C. § 154(b)(1)(B), is the date that is 30 months from the priority date of the International application (i.e., September 29, 2004), as explained hereinbelow. Therefore, Plaintiff contends that a total USPTO prosecution delay under 35 U.S.C. § 154(b)(1)(B) should be 668 days, calculated from September 29, 2007 (the date that is three years from the "actual filing date" of the '728 Patent (September 29, 2004)) through to the grant date on July 28, 2009.

More specifically, 35 U.S.C. § 154(b)(1)(B) states:

> (B) GUARANTEE OF NO MORE THAN 3-YEAR APPLICATION PENDENCY.- Subject to the limitations under paragraph (2), if the issue of an original patent is delayed due to the failure of the United States Patent and Trademark Office to issue a patent within 3 years after the actual filing date of the application in the United States,...(emphasis added.)

In addition, 37 C.F.R. § 1.702(b) explains the meaning of the term "actual filing date" as used in 35 U.S.C. § 154(b)(1)(B). In particular, 37 C.F.R. § 1.702(b) states:

> (b) *Failure to issue a patent within three years of the actual filing date of the application.* Subject to the provisions of 35 U.S.C. 154(b) and

> this subpart, the term of an original patent shall be adjusted if the issuance of the patent was delayed due to the failure of the Office to issue a patent within three years after the date on which the application was filed under 35 U.S.C. 111(a) or the national stage commenced under 35 U.S.C. 371(b) or (f) in an international application,...(emphasis added.)

Furthermore, 35 U.S.C. §§ 371(b) and (f) refer to the time when a national stage application "commences" as follows:

> (b) Subject to subsection (f) of this section, the national stage shall commence with the expiration of the applicable time limit under article 22 (1) or (2), or under article 39 (1)(a) of the treaty. (emphasis added.)
>
> ....
>
> (f) At the express request of the applicant, the national stage of processing may be commenced at any time at which the application is in order for such purpose and the applicable requirements of subsection (c) of this section have been complied with. (emphasis added.)

In other words, unless an express request of the applicant is filed and the applicable requirements of 35 U.S.C. § 371(c) have been complied with, the U.S. national stage commences under 35 U.S.C. § 371(b), i.e., with the expiration of the applicable time limit under Article 22 (1) or (2), or under Article 39 (1)(a) of the Patent Cooperation Treaty.

Moreover, Article 22 (1) and (2) and Article 39(1)(a) state:

> Article 22
>
> Copy, Translation, and Fee, to Designated Offices
>
> (1) The applicant shall furnish a copy of the international application (unless the communication provided for in Article 20 has already taken place) and a translation thereof (as prescribed), and pay the national fee (if any), to each designated Office not later than at the expiration of 30 months from the priority date. Where the national

law of the designated State requires the indication of the name of and other prescribed data concerning the inventor but allows that these indications be furnished at a time later than that of the filing of a national application, the applicant shall, unless they were contained in the request, furnish the said indications to the national Office of or acting for the State not later than at the expiration of 30 months from the priority date. (emphasis added.)

(2) Where the International Searching Authority makes a declaration, under Article 17(2)(a), that no international search report will be established, the time limit for performing the acts referred to in paragraph (1) of this Article shall be the same as that provided for in paragraph (1).

Article 39

Copy, Translation, and Fee, to Elected Offices

(1) (a) If the election of any Contracting State has been effected prior to the expiration of the 19th month from the priority date, the provisions of Article 22 shall not apply to such State and the applicant shall furnish a copy of the international application (unless the communication under Article 20 has already taken place) and a translation thereof (as prescribed), and pay the national fee (if any), to each elected Office not later than at the expiration of 30 months from the priority date. (emphasis added.)

In other words, "the applicable time limit under article 22 (1) or (2), or under article 39 (1)(a) of the treaty " stated in 35 U.S.C. § 371(b) is the expiration of 30 months from the priority date. Therefore, the expiration of 30 months from the priority date is the time at which the U.S. national stage shall commence under 35 U.S.C. § 371(b).

In view of the above, in the absence of filing an express request under 35 U.S.C. § 371(f), the "actual filing date" of a U.S. national stage application filed under 35 U.S.C. § 371, for the purpose of calculating the USPTO's delay under 35 U.S.C. §

154(b)(1)(B), is the date that is 30 months from the earliest priority date of the international application.

Since no express request under 35 U.S.C. § 371(f) was filed during prosecution of the '728 Patent, the "actual filing date" of the '728 Patent, for the purpose of calculating the USPTO's delay under 35 U.S.C. § 154(b)(1)(B), is the date that is 30 months from the priority date of the International application (i.e., September 29, 2004).

Therefore, Plaintiff contends that a total USPTO prosecution delay under 35 U.S.C. § 154(b)(1)(B) should be 668 days, calculated from September 29, 2007 (the day that is three years from the "actual filing date" of the '728 Patent (i.e., September 29, 2004)) through to the grant date on July 28, 2009.

21. **No Overlap of USPTO's Delay under 35 U.S.C. § 154(b)(2)(A)**

Under *Wyeth v. Dudas* and the subsequent affirmance of this decision by the United States Court of Appeals for the Federal Circuit in *Wyeth v. Kappos*, the only way that the USPTO prosecution delay under 35 U.S.C. § 154(b)(1)(A) and the USPTO prosecution delay under 35 U.S.C. § 154(b)(1)(B) can overlap under 35 U.S.C. § 154(b)(2)(A) is if they occur on the same day.

Plaintiff contends that there is no overlap of USPTO prosecution delay under 35 U.S.C. § 154(b)(2)(A) because the entire USPTO prosecution delay under 35 U.S.C. § 154(b)(1)(A) occurred between December 25, 2005 and July 23, 2007 (see paragraph 19, above), which was prior to any USPTO prosecution delay under 35 U.S.C. § 154(b)(1)(B) starting from September 29, 2007 (i.e.,

three (3) years after the "actual filing date" of September 29, 2004).

22. **Applicant's Delay under 35 U.S.C. § 154(b)(1)(B)**

Plaintiff concedes a 64-day delay under 35 U.S.C. § 154(b)(1)(B) for the response filed December 26, 2007 to the Office Action issued July 23, 2007, and a 34-day delay for the Supplemental Response filed January 15, 2009 to the final Office Action issued September 12, 2008. In other words, Plaintiff concedes that the delay by Applicant under 35 U.S.C. § 154(b)(1)(B) is 98 days (64+34 days) for the '728 Patent.

In addition, the USPTO originally erroneously determined that the delay by Applicant under 35 U.S.C. § 154(b)(1)(B) is 102 days (64+38 days) for the '728 Patent. On April 28, 2009, Plaintiff filed a Petition for Request for Reconsideration of Patent Term Adjustment under 37 C.F.R. § 1.705, arguing that the delay by Applicant under 35 U.S.C. § 154(b)(1)(B) should be 98 days. The USPTO in the Petition Decision dated June 22, 2009 correctly determined that the delay by Applicant under 35 U.S.C. § 154(b)(1)(B) is 98 days (64+34 days) for the '728 Patent, which is consistent with what Plaintiff concedes.

23. **Total PTA**

The total PTA should be calculated as follows:

PTA = USPTO's delay under 35 U.S.C. § 154(b)(1)(A) + USPTO's delay under 35 U.S.C. § 154(b)(1)(B) – Overlap under 35 U.S.C. § 154(b)(2)(A) – Applicant's delay under 35 U.S.C. § 154(b)(1)(B) = 575 + 668 – 0 – 98 = 1145 days.

24. The USPTO's grant of only 544 days of PTA for the '728 Patent is arbitrary, capricious, and an abuse of discretion, or is otherwise not in accordance with law and in excess of statutory jurisdiction, authority or limitation.

25. It is accordingly believed that the overall PTA accrued by the Plaintiff is **1145 days**, and the patent holder accordingly requests **601 ADDITIONAL days** of PTA.

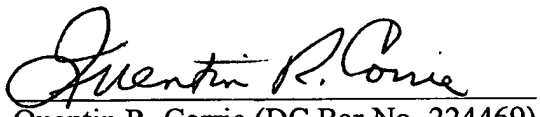
WHEREFORE, Plaintiff respectfully pray that this Court:

A. Issue an Order changing the period of PTA for the '728 Patent term from 544 days to 1145 days and requiring Defendant to alter the terms of the '728 Patent to reflect the 1145 days of actual PTA due the '728 Patent.

B. Grant such other and further relief as the nature of the case may admit or require and as may be just and equitable.

Dated: January 22, 2010

Respectfully submitted,



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US007566728B2

(12) **United States Patent**
Teshima et al.

(10) **Patent No.: US 7,566,728 B2**
(45) **Date of Patent: Jul. 28, 2009**

(54) **REMEDY FOR SLEEP DISTURBANCE**

(75) Inventors: **Koji Teshima**, Tokyo (JP); **Masanori Minoguchi**, Tokyo (JP)

(73) Assignee: **Mitsubishi Tanabe Pharma Corporation**, Osaka (JP)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 544 days.

(21) Appl. No.: **10/508,339**

(22) PCT Filed: **Mar. 28, 2003**

(86) PCT No.: **PCT/JP03/03925**

§ 371 (c)(1),
(2), (4) Date: **Oct. 25, 2004**

(87) PCT Pub. No.: **WO03/082333**

PCT Pub. Date: **Oct. 9, 2003**

(65) **Prior Publication Data**

US 2005/0119308 A1 Jun. 2, 2005

(30) **Foreign Application Priority Data**

Mar. 29, 2002 (JP) 2002-093398

(51) **Int. Cl.**
A61K 31/454 (2006.01)

(52) **U.S. Cl.** **514/322**; 546/199

(58) **Field of Classification Search** 514/310, 514/322

See application file for complete search history.

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Primary Examiner—Rita J Desai
Assistant Examiner—David K O'Dell
(74) *Attorney, Agent, or Firm*—Wenderoth, Lind & Ponack, L.L.P.

(57) **ABSTRACT**

The present invention has been made based on the finding that a compound acting on the ORL-1 receptor as an agonist acts as a non-photic entrainment factor, and advances the circadian rhythm phase, and provides a novel therapeutic agent for a sleep disorder such as circadian rhythm sleep disorder, more particularly, an agent for the prophylaxis and/or treatment of a sleep disorder, which contains an ORL-1 receptor agonist, and a novel compound useful as such agent for the prophylaxis and/or treatment.

5 Claims, 4 Drawing Sheets

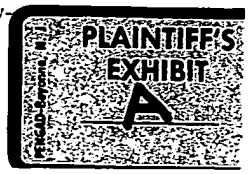

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FIG. 1

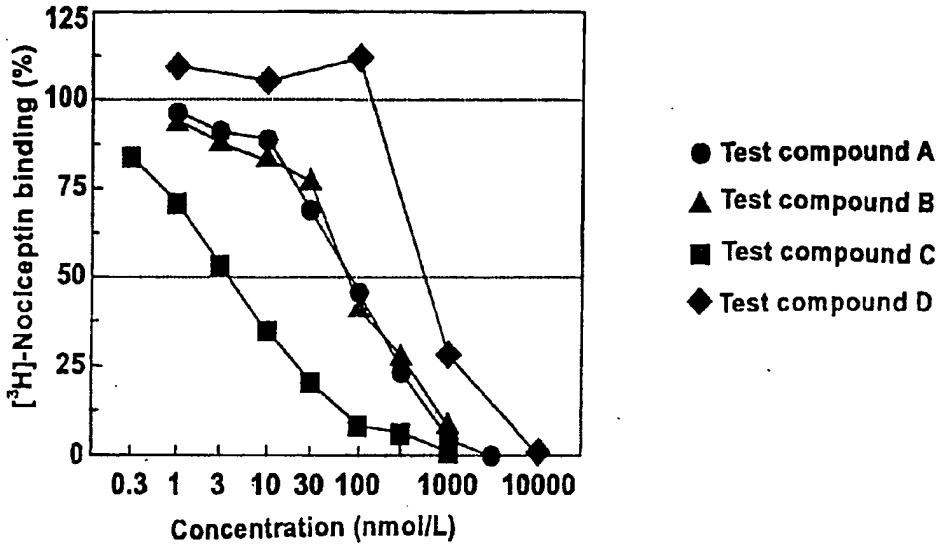

125
100
75
50
25
0
[3H]-Nociceptin binding (%)
0.3 1 3 10 30 100 1000 10000
Concentration (nmol/L)
Test compound A
Test compound B
Test compound C
Test compound D

FIG. 2

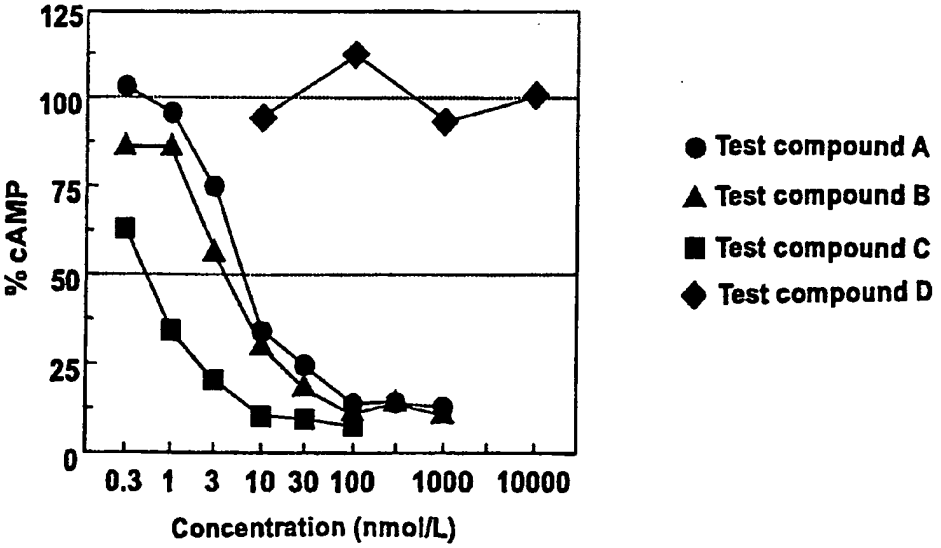
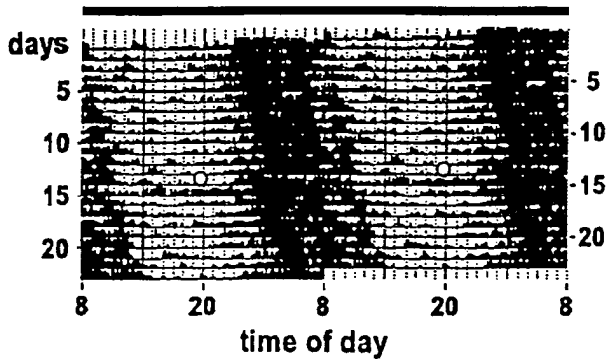
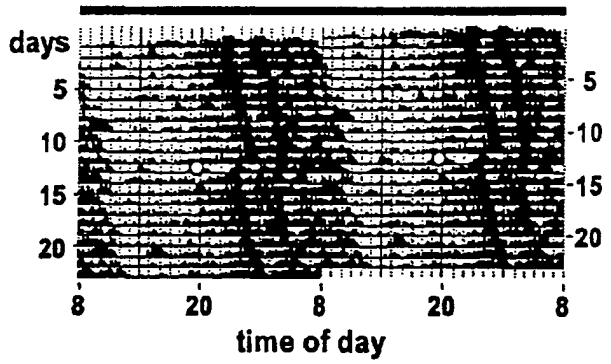

125
100
75
50
25
0
% cAMP
0.3 1 3 10 30 100 1000 10000
Concentration (nmol/L)
Test compound A
Test compound B
Test compound C
Test compound D

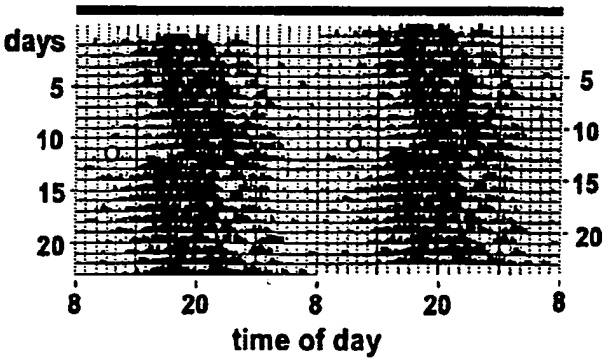
FIG. 3



Test compound A
10 mg/kg, i.p. (CT6)



Test compound B
3 mg/kg, i.p. (CT6)



Test compound C
3 mg/kg, i.p. (CT6)

FIG. 4

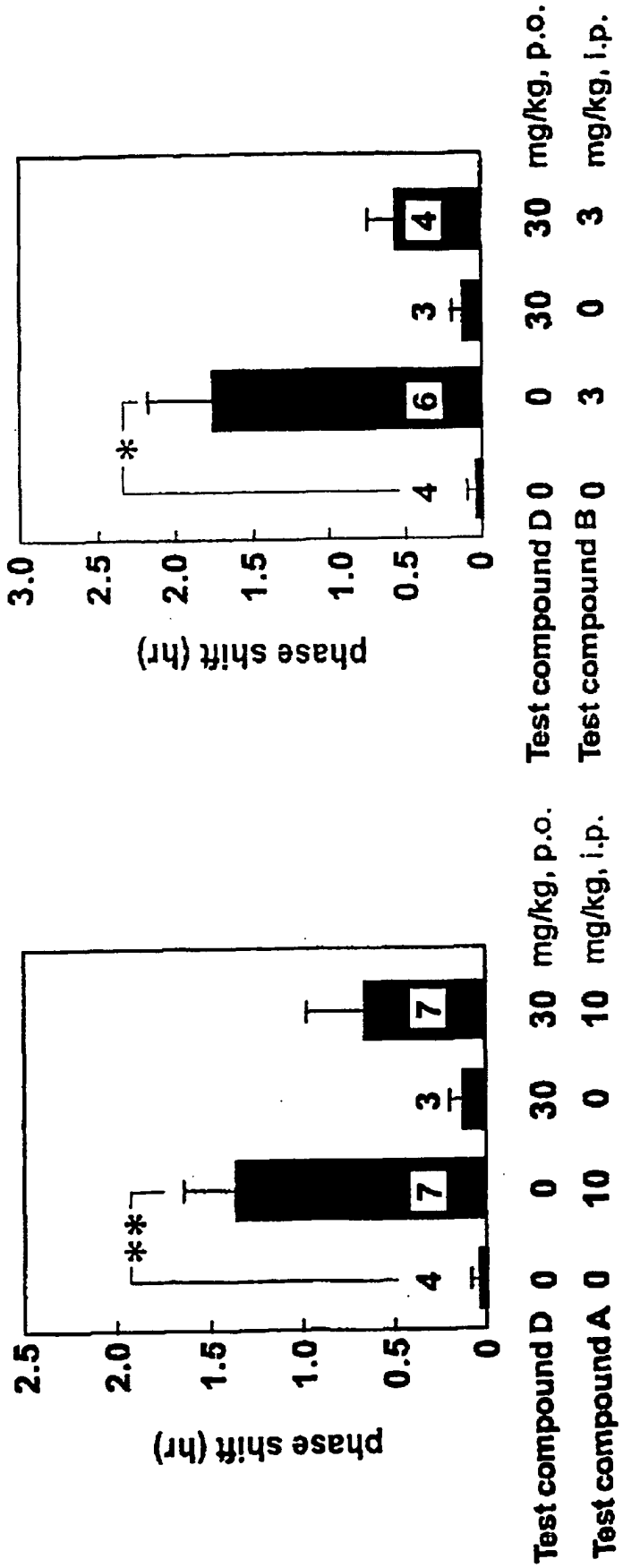
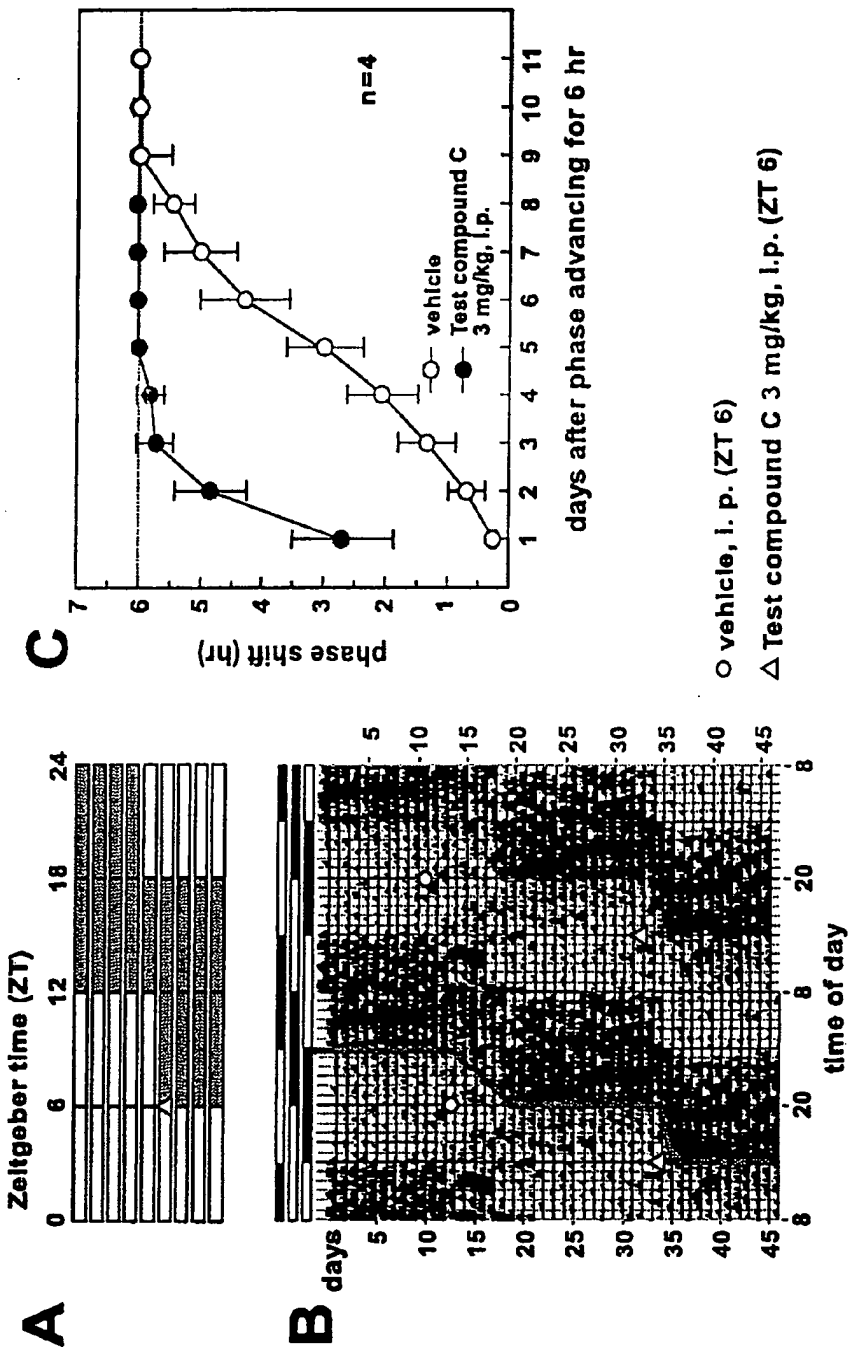

phase shift (hr)
3.0
2.5
2.0
1.5
1.0
0.5
0
*
4
6
3
4
Test compound D 0 0 30 30 mg/kg, p.o.
Test compound B 0 3 0 3 mg/kg, i.p.
phase shift (hr)
2.5
2.0
1.5
1.0
0.5
0
**
4
7
3
7
Test compound D 0 0 30 30 mg/kg, p.o.
Test compound A 0 10 0 10 mg/kg, i.p.

FIG. 5


A
Zeitgeber time (ZT)
0
6
12
18
24
B
days
5
10
15
20
25
30
35
40
45
time of day
8
20
8
20
8
C
phase shift (hr)
0
1
2
3
4
5
6
7
days after phase advancing for 6 hr
1 2 3 4 5 6 7 8 9 10 11
n=4
vehicle
Test compound C
3 mg/kg, i.p.
○ vehicle, i. p. (ZT 6)
△ Test compound C 3 mg/kg, i.p. (ZT 6)

REMEDY FOR SLEEP DISTURBANCE

This application is a U.S. national stage of International Application No. PCT/JP03/03925 filed Mar. 28, 2003.

TECHNICAL FIELD

The present invention relates to a medicament useful for treating and/or preventing a sleep disorder. More specifically, the present invention relates to a medicament containing an ORL-1 receptor agonist which is useful for treating and/or preventing a sleep disorder, for example, a circadian rhythm sleep disorder such as jet-lag syndromes, a shift-work sleep disorder, delayed sleep phase syndromes or the like.

BACKGROUND ART

An ORL-1 (opioid receptor-like 1) receptor (FEBS Lett. 347, 284-288, 1994, FEBS Lett. 341, 33-38, 1994) was found to be a fourth opioid receptor next to δ, κ and μ receptors in 1994. The ORL-1 receptor has about 60% homology of amino acid sequences with other opioid receptors, but it is clearly distinguished from other opioid receptors in that naloxone, a non-selective opioid receptor antagonist, does not bind thereto (FEBS Lett. 341, 33-38, 1994). The ORL-1 receptor is mainly distributed in a central nerve system broadly, and is expressed in high density especially in a cerebral cortex, hippocampus, hypothalamus, amygdala and spinal cord, though it is also expressed in peripheral organs such as intestine and spleen (Eur. J. Pharmacol. 340, 1-15, 1997, Pharmacol. Rev. 53, 381-415, 2001).

Endogenous ligands for the ORL-1 receptor were identified successively by the research groups in France and Switzerland in 1995, and were designated as nociceptin (Nature 377, 532-535, 1995) and orphanin FQ (Science 270, 792-794, 1995), respectively. Nociceptin has been reported to be a peptide consisting of 17 amino acids, and plays a critical role in central functions such as learning, memory, anxiety and stress (Br. J. Pharmacol. 129, 1261-1283, 2000).

Specifically, it has been reported that injecting a small amount of nociceptin to hippocampus of rats causes learning disorder in water-maze learning test (Eur. J. Neurosci. 9, 194-197, 1997) and the nociceptin receptor knock-out mice are quick in learning acquisition in water-maze learning test as compared to normal mice (wild-type), and that long term potentiation (LTP) in hippocampus of knock-out mouse is enhanced as compared to normal mice (Nature 394, 577-581, 1998). Nociceptin is considered to inhibit memory and/or learning functions. In addition, it has been reported that if nociceptin is administered intraventricularly in rats, the anti-anxiety activity is found to be almost equivalent to diazepam in a behavioral pharmacology test such as a conflict test, a light-dark box test and an elevated plus maze test (Proc. Natl. Acad. Sci. USA 94, 14854-14858, 1997). Further, it has been reported that the sensitivity to stress is enhanced, and the adaptation ability to stress is inhibited in nociceptin knock-out mice as compared to normal mice (Proc. Natl. Acad. Sci. USA 96, 10444-10449, 1999). In other words, nociceptin is considered to have a defensive physiological action against anxiety or stress, and the ORL-1 receptor agonist is likely to show anti-anxiety actions by a completely different mechanism from benzodiazepine compounds.

From the above, it has been reported that a compound having an agonistic and/or antagonistic activity for the ORL-1 receptor, is useful for treating a mental disorder, a neural disorder and a physiological disorder, and in particular for improving anxiety and stress disorders, depression, a trauma disorder, memory loss from Alzheimer's disease or other dementia, epilepsy and spasm symptoms, acute and/or chronic pain symptoms, withdrawal symptoms from drug addiction, control of water balance, Na^+ excretion, arterial blood pressure disorder and eating disorder such as obesity and anorexia (publications such as JP-A-2000-26466, JP-A-11-228575, JP-A-10-212290, JP-A-2000-53686, WO00/14067, WO99/29696, EP1122257, JP-A-2001-39974, WO00/08013, WO99/36421, EP0997464, WO03/000677, WO98/54168, WO00/31061, JP-A-2001-58991, WO01/39767, WO01/39775, WO02/085291, WO02/085354, WO02/085355, WO02/085361, WO00/27815, WO00/06545, WO99/59997, WO99/48492, WO02/26714, etc.).

On the other hand, the circadian rhythm sleep disorder is a disease in which a person's main complaint or cardinal symptom is the lack of normal sleep at night, and this disease may sometimes disturb ordinary social behavior. This disease includes a variety of pathological states, for example, endogenous chronic syndromes such as delayed sleep phase syndromes caused by a disruption of the biological clock and its synchronizing mechanism, as well as exogenous acute syndromes such as jet-lag syndromes and a shift-work sleep disorder. Although various drug therapies have been tried for the treatment of circadian rhythm sleep disorder, it has been revealed that only an insufficient therapeutic effect can be obtained with hypnotics, which are typically benzodiazepine hypnotics (as a Review of pathologic states, therapy or others for a circadian rhythm sleep disorder, see, for example, S. Ozaki and K. Okawa, "Sleep Disorder and Biological Rhythm", Special feature; Chronopharmacology, New Guideline of Administration, Molecular Medicine, Vol.34(3), pp. 355-365, 1997, etc.).

Entrainment factors of circadian rhythm are classified into the two major groups of light (photic entrainment) and other factors than light (non-photic entrainment). The drugs which have been known to cause non-photic entrainment so far, are serotonin agonists, benzodiazepine hypnotics, melatonin and the like, but no ORL-1 receptor agonist has been reported to cause non-photic entrainment. One paper has disclosed that a small amount of nociceptin, an endogenous ligand of the ORL-1 receptor, was injected into suprachiasmatic nucleus, biological clock of hamster, but the paper has concluded that nociceptin inhibits photic entrainment, but nociceptin itself does not cause non-photic entrainment (J. Neurosci., Vol.19 (6), pp. 2152-2160, 1999).

In addition, the above-mentioned publications and the patent publication neither disclose nor suggest that a compound having an agonistic and/or antagonistic activity for the ORL-1 receptor, can be used for treating a circadian rhythm sleep disorder.

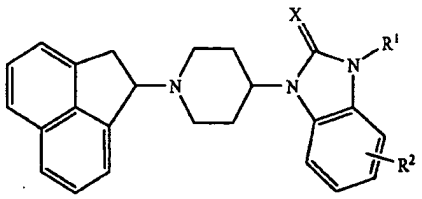
DISCLOSURE OF THE INVENTION

As described above, the relation of the ORL-1 receptor and the circadian rhythm has not been fully clarified, but the present inventors have found unexpectedly that a compound having an affinity for the ORL-1 receptor, in particular a compound acting on the ORL-1 receptor as an agonist, acts as a non-photic entrainment factor, and advances the circadian rhythm phase. In other words, the present inventors have made extensive researches with the purpose of developing a novel therapeutic agent for circadian rhythm sleep disorder, and have found that ORL-1 receptor agonist can be a preventive and/or therapeutic agent for a sleep disorder including the circadian rhythm sleep disorder, which resulted in the completion of the present invention.

The present invention relates to a medicament useful for treating and/or preventing a sleep disorder. More specifically, the present invention provides a medicament containing an ORL-1 receptor agonist which is useful for preventing and/or treating a sleep disorder, for example, a circadian rhythm sleep disorder such as jet-lag syndromes, a shift-work sleep disorder, or delayed sleep phase syndromes, and a novel compound having an ORL-1 receptor agonist action.

Specifically, the present invention provides the following.

1. A preventive and/or therapeutic agent for a sleep disorder containing an ORL-1 receptor agonist.
2. A preventive and/or therapeutic agent for a sleep disorder comprising a therapeutically effective amount of an ORL-1 receptor agonist and pharmaceutically acceptable additives.
3. The preventive and/or therapeutic agent as described in the above-mentioned 1 or 2, wherein the sleep disorder is a circadian rhythm sleep disorder.
4. The preventive and/or therapeutic agent as described in the above-mentioned 3, wherein the circadian rhythm sleep disorder is a jet-lag syndrome.
5. The preventive and/or therapeutic agent as described in the above-mentioned 3, wherein the circadian rhythm sleep disorder is shift-work sleep disorder.
6. The preventive and/or therapeutic agent as described in the above-mentioned 3, wherein the circadian rhythm sleep disorder is a delayed sleep phase syndrome.
7. The preventive and/or therapeutic agent as described in the above-mentioned 1 or 2, used for preventing and/or treating the symptoms involved in a geriatric circadian rhythm sleep disorder.
8. The preventive and/or therapeutic agent as described in the above-mentioned 1 or 2, used for bright light therapy.
9. The preventive and/or therapeutic agent as described in the above-mentioned 1 or 2, wherein the ORL-1 receptor agonist has an affinity of 1000 nmol/L or less IC_{50} value for the ORL-1 receptor, and further inhibits cAMP elevation caused by a cAMP inducer by 50% or more at a concentration of 1000 nmol/L or less.
10. A compound represented by the formula (I)



(I)

wherein

R^1 is

(1) hydrogen,
(2) lower alkyl,
(3) lower alkenyl,
(4) —C(O)-lower alkyl,
(5) —C(O)O-lower alkyl,
(6) —C(O)-phenyl (the phenyl group may be substituted with lower alkyl, halogen, lower alkoxy, phenoxy or benzyloxy),
(7) lower alkyl-carboxyl,
(8) lower alkyl-C(O)-phenyl (the phenyl group may be substituted with lower alkyl, halogen, lower alkoxy, phenoxy or benzyloxy),
(9) lower alkyl-C(O)O-lower alkyl,
(10) lower alkenyl-C(O)O-lower alkyl,
(11) lower alkyl-O-lower alkyl,
(12) lower alkyl-C(O)NR^3R^4,
(13) —$S(O)_2$-lower alkyl,
(14) —$S(O)_2$-phenyl (the phenyl group may be substituted with lower alkyl, halogen, lower alkoxy, phenoxy or benzyloxy),
(15) lower alkyl-S-lower alkyl,
(16) lower alkyl-S(O)-lower alkyl,
(17) lower alkyl-$S(O)_2$-lower alkyl,
(18) lower alkyl-$S(O)_2NR^3R^4$,
(19) phenyl (the phenyl group may be substituted with lower alkyl, halogen, lower alkoxy, phenoxy or benzyloxy), or
(20) benzyl (the phenyl group may be substituted with lower alkyl, halogen, lower alkoxy, phenoxy or benzyloxy),

R^2 is hydrogen, lower alkyl, halogen, lower alkoxy, phenoxy, benzyloxy, trifluoromethyl, nitro, amino or cyano,

R^3 and R^4 may be the same or different, and each is hydrogen, lower alkyl or lower alkenyl, or R^3 and R^4 may bind with an adjacent nitrogen atom to form a saturated nitrogen-containing hetero ring (the hetero ring may be substituted with lower alkyl, halogen, lower alkoxy, phenoxy or benzyloxy), and

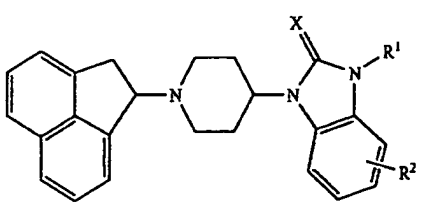
X is O or S.),

a racemic mixture thereof, an enantiomer corresponding thereto, or a pharmaceutically acceptable salt thereof.

11. The compound as described in the above-mentioned 10, wherein R^2 is hydrogen, and X is O.
12. The compound as described in the above-mentioned 10, wherein R^1 is —C(O)-lower alkyl, lower alkyl-C(O)NR^3R^4 (either R^3 or R^4 is hydrogen) or lower alkyl-C(O)NR^3R^4 [R^3 and R^4 bind with an adjacent nitrogen atom to form a saturated nitrogen-containing hetero ring (the hetero ring may be substituted with lower alkyl, halogen, lower alkoxy, phenoxy or benzyloxy)].
13. The compound as described in the above-mentioned 10, which is selected from

(RS)-1-[1-(acenaphthen-1-yl)piperidin-4-yl]-1,3-dihydro-2H-benzoimidazol-2-one,
(R)-1-[1-(acenaphthen-1-yl)piperidin-4-yl]-1,3-dihydro-2H-benzoimidazol-2-one,
(S)-1-[1-(acenaphthen-1-yl)piperidin-4-yl]-1,3-dihydro-2H-benzoimidazol-2-one,
(R)-3-acetyl-1-[1-(acenaphthen-1-yl)piperidin-4-yl]-1,3-dihydro-2H-benzoimidazol-2-one,
(R)-2-{3-[1-(acenaphthen-1-yl)piperidin-4-yl]-2,3-dihydro-2-oxo-benzoimidazol-1-yl}-N-methylacetamide, and
(R)-1-[1-(acenaphthen-1-yl)piperidin-4-yl]-3-(2-oxo-2-piperazin-1-ylethyl)-1,3-dihydro-2H-benzoimidazol-2-one.

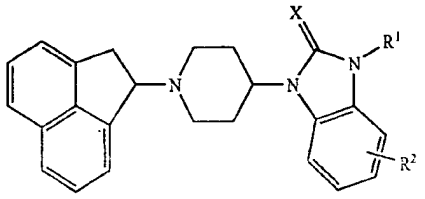
14. The preventive and/or therapeutic agent as described in the above-mentioned 1 or 2, wherein the ORL-1 receptor agonist is a compound represented by the formula (I)



(I)

wherein each symbol is as defined above, a racemic mixture thereof, an enantiomer corresponding thereto, or a pharmaceutically acceptable salt thereof.

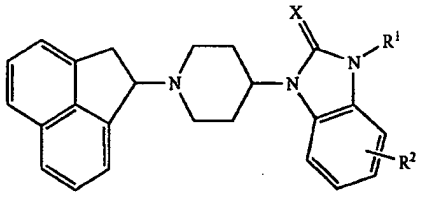
15. A method of preventing and/or treating a sleep disorder, comprising administering an effective amount of an ORL-1 receptor agonist to the patients.
16. The method as described in the above-mentioned 15, wherein the ORL-1 receptor agonist has an affinity of 1000 nmol/L or less IC_{50} value for ORL-1 receptor, and further inhibits cAMP elevation caused by a cAMP inducer by 50% or more at a concentration of 1000 nmol/L or less.
17. The method as described in the above-mentioned 15, wherein the ORL-1 receptor agonist is a compound represented by the formula (I)



(I)

wherein each symbol is as defined above, a racemic mixture thereof, an enantiomer corresponding thereto, or a pharmaceutically acceptable salt thereof.

18. Use of an ORL-1 receptor agonist for manufacturing a preventive and/or therapeutic agent for a sleep disorder.
19. The use as described in the above-mentioned 18, wherein ORL-1 receptor agonist has an affinity of 1000 nmol/L or less IC_{50} value for ORL-1 receptor, and further inhibits cAMP elevation caused by a cAMP inducer by 50% or more at a concentration of 1000 nmol/L or less.
20. The use as described in the above-mentioned 18, wherein ORL-1 receptor agonist is a compound represented by the formula (I)



(I)

wherein each symbol is as defined above, a racemic mixture thereof, an enantiomer corresponding thereto, or a pharmaceutically acceptable salt thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 shows the results of an ORL-1 receptor binding test.

FIG. 2 shows the results of a cAMP assay.

FIG. 3 shows a typical example of a phase shift of a circadian rhythm in rats by test compounds A, B and C, as ORL-1 receptor agonists.

FIG. 4 shows actions of a test compound D, an ORL-1 receptor antagonist on phase advancing circadian rhythm in rats by test compounds A and B, as ORL-1 receptor agonists.

FIG. 5 shows actions of a test compound C as an ORL-1 receptor agonist on re-entrainment after a 6-hour advancement of a light-dark cycle. A: shift of the light-dark cycle and an administration timing, B: a typical example of a body-temperature rhythm re-entrainment, and C: summary of results of 4 examples.

DETAILED DESCRIPTION OF THE INVENTION

An "ORL-1 receptor agonist" in the present invention refers to a compound having an agonistic activity for an ORL-1 receptor. The ORL-1 receptor agonist is preferably a compound having an affinity of 1000 nmol/L or less IC_{50} value for the ORL-1 receptor, and further inhibits cAMP elevation caused by a cAMP (cyclic adenosine monophosphate) inducer such as forskolin and isoproterenol by 50% or more at a concentration of 1000 nmol/L or less. The present invention comprises both of a full agonist and a partial agonist for the ORL-1 receptor.

Definitions of each symbol in the formula (I) are as follows. In the present specification, the definitions apply irrespective of whether the terms appear alone or in a combination.

"Lower alkyl" means a straight or branched alkyl group containing 1 to 6 carbon atoms, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, secondary butyl, tertiary butyl, pentyl, hexyl and the like. Lower alkyl is preferably a straight or branched alkyl group containing 1 to 4 carbon atoms.

"Lower alkenyl" means, straight or branched alkenyl containing 2 to 6 carbon atoms, for example, vinyl, 1-propenyl, 2-propenyl, isopropenyl, 1-butenyl, 2-butenyl, 3-butenyl and the like. Lower alkenyl is preferably a straight or branched alkenyl group containing 2 to 4 carbon atoms.

"Halogen" means chlorine, iodine, fluorine and bromine. Halogen is preferably fluorine.

"Lower alkoxy" means a straight or branched alkoxy group containing 1 to 6 carbon atoms, for example, methoxy, ethoxy, propoxy, isopropoxy, butoxy and the like. Lower alkoxy is preferably a straight or branched alkoxy group containing 1 to 4 carbon atoms.

A "saturated nitrogen-containing hetero ring formed by binding with an adjacent nitrogen atom", means a 5- or 6-membered ring which may further contain 1 to 3 heteroatoms selected from a nitrogen atom, an oxygen atom and a sulfur atom, for example, piperidine, pyrrolidine, morpholine, thiomorpholine, piperadine, methyl piperadine and the like. Piperadine and morpholine are preferred.

"—C(O)—" means a carbonyl group.

"—S(O)—" means a sulfinyl group.

"—$S(O)_2$—" means a sulfonyl group.

A "pharmaceutically acceptable salt" comprises an acid-addition salt with an inorganic acid and an organic acid such as chloric acid, oxalic acid, fumaric acid and the like, and a salt with an inorganic base such as sodium, potassium, calcium, magnesium and the like.

If the phenyl group and the saturated nitrogen-containing hetero ring formed by binding with an adjacent nitrogen atom in the formula (I) are substituted with lower alkyl, halogen, lower alkoxy, phenoxy or benzyloxy, the number of the substituent is preferably 1 to 3.

The compound is preferably a compound wherein R^1 is hydrogen, lower alkyl, —C(O)-lower alkyl, lower alkyl-carboxyl, lower alkyl-C(O)O-lower alkyl or lower alkyl-C(O)NR^3R^4, or —$S(O)_2$-lower alkyl, R^2 is hydrogen or halogen, R^3 and R^4 are hydrogen or lower alkyl, or R^3 and R^4 bind with an adjacent nitrogen atom to form a saturated nitrogen-containing hetero ring (the hetero ring may be substituted with

lower alkyl, halogen, lower alkoxy, phenoxy or benzyloxy), and X is O or S. Examples of preferred compound are as follows.

[1] (RS)-1-[1-(acenaphthen-1-yl)piperidin-4-yl]-1,3-dihydro-2H-benzoimidazol-2-one,

[2] (RS)-1-[1-(acenaphthen-1-yl)piperidin-4-yl]-1,3-dihydro-5-fluoro-2H-benzoimidazol-2-one,

[3] (RS)-1-[1-(acenaphthen-1-yl)piperidin-4-yl]-1,3-dihydro-6-fluoro-2H-benzoimidazol-2-one,

[4]ethyl (RS)-2-{3-[1-(acenaphthen-1-yl)piperidin-4-yl]-2,3-dihydro-2-oxo-benzoimidazol-1-yl}acetate,

[5] (RS)-2-{3-[1-(acenaphthen-1-yl)piperidin-4-yl]-2,3-dihydro-2-oxo-benzoimidazol-1-yl}acetic acid,

[6] (RS)-1-[1-(acenaphthen-1-yl)piperidin-4-yl]-3-(2-oxo-2-piperazin-1-ylethyl)-1,3-dihydro-2H-benzoimidazol-2-one dihydrochloride,

[7] (RS)-1-[1-(acenaphthen-1-yl)piperidin-4-yl]-3-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-1,3-dihydro-2H-benzoimidazol-2-one dihydrochloride,

[8] (RS)-1-[1-(acenaphthen-1-yl)piperidin-4-yl]-3-(2-morpholin-4-yl-2-oxoethyl)-1,3-dihydro-2H-benzoimidazol-2-one hydrochloride,

[9] (RS)-1-[1-(acenaphthen-1-yl)piperidin-4-yl]-1,3-dihydro-2H-benzoimidazole-2-thione,

[10] (RS)-1-[1-(acenaphthen-1-yl)piperidin-4-yl]-1,3-dihydro-3-methyl-2H-benzoimidazole-2-thione,

[11] (R)-1-[1-(acenaphthen-1-yl)piperidin-4-yl]-1,3-dihydro-2H-benzoimidazol-2-one,

[12] (S)-1-[1-(acenaphthen-1-yl)piperidin-4-yl]-1,3-dihydro-2H-benzoimidazol-2-one,

[13] (R)-3-acetyl-1-[1-(acenaphthen-1-yl)piperidin-4-yl]-1,3-dihydro-2H-benzoimidazol-2-one,

[14] (R)-1-[1-(acenaphthen-1-yl)piperidin-4-yl]-3-methanesulfonyl-1,3-dihydro-2H-benzoimidazol-2-one,

[15]ethyl (R)-2-(3-[1-(acenaphthen-1-yl)piperidin-4-yl]-2,3-dihydro-2-oxo-benzoimidazol-1-yl)acetate,

[16] (R)-2-{3-[1-(acenaphthen-1-yl)piperidin-4-yl]-2,3-dihydro-2-oxo-benzoimidazol-1-yl}acetic acid,

[17] (R)-1-[1-(acenaphthen-1-yl)piperidin-4-yl]-3-(2-oxo-2-piperazin-1-ylethyl)-1,3-dihydro-2H-benzoimidazol-2-one dihydrochloride,

[18] (R)-2-{3-[1-(acenaphthen-1-yl)piperidin-4-yl]-2,3-dihydro-2-oxo-benzoimidazol-1-yl}-N-methylacetamide,

[19] (R)-2-{3-[1-(acenaphthen-1-yl)piperidin-4-yl]-2,3-dihydro-2-oxo-benzoimidazol-1-yl}-N,N-dimethylacetamide, and

[20] (R)-2-{3-[1-(acenaphthen-1-yl)piperidin-4-yl]-2,3-dihydro-2-oxo-benzoimidazol-1-yl}acetamide.

Particularly preferred compound is a compound wherein R^1 is hydrogen, —C(O)-lower alkyl or lower alkyl-C(O)NR^3R^4 (either R^3 or R^4 is hydrogen) or lower alkyl-C(O)NR^3R^4 (R^3 and R^4 bind with an adjacent nitrogen atom to form a saturated nitrogen-containing hetero ring (the hetero ring may be substituted with lower alkyl, halogen, lower alkoxy, phenoxy or benzyloxy)), R^2 is hydrogen and X is O. Examples of especially preferred compound are as follows.

(RS)-1-[1-(acenaphthen-1-yl)piperidin-4-yl]-1,3-dihydro-2H-benzoimidazol-2-one,

(R)-1-[1-(acenaphthen-1-yl)piperidin-4-yl]-1,3-dihydro-2H-benzoimidazol-2-one,

(S)-1-[1-(acenaphthen-1-yl)piperidin-4-yl]-1,3-dihydro-2H-benzoimidazol-2-one,

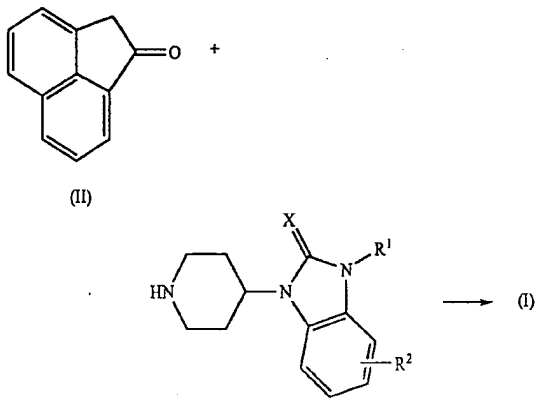
(R)-3-acetyl-1-[1-(acenaphthen-1-yl)piperidin-4-yl]-1,3-dihydro-2H-benzoimidazol-2-one,

(R)-2-{3-[1-(acenaphthen-1-yl)piperidin-4-yl]-2,3-dihydro-2-oxo-benzoimidazol-1-yl}-N-methylacetamide, and

(R)-1-[1-(acenaphthen-1-yl)piperidin-4-yl]-3-(2-oxo-2-piperadin-1-ylethyl)-1,3-dihydro-2H-benzoimidazol-2-one.

The compound of the formula (I) can be prepared, for example, by the following methods.

Method 1

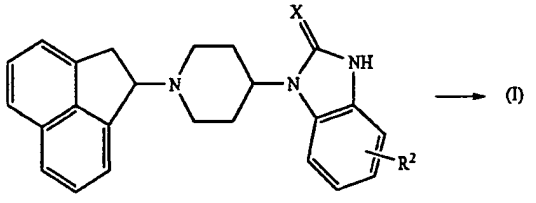


wherein each symbol is as defined above.

A compound of the formula (II) is reductively aminated by a compound of the formula (III) to obtain a compound of the formula (I). The compound of the formula (II) and the compound of the formula (III) are known compounds. The compound of the formula (II) can be prepared by the method described in J. Chem. Soc., Perkin Trans 1, 1160, 1973, and the compound of the formula (III) can be prepared by the method described in J. Med. Chem., 2001, 44, 3378.

Reductive amination of a keto compound of the formula (II) with amine such as the compound of the formula (III) is described in J. Org. Chem., 55, 2552-54, 1990. The present reaction according to this method is carried out by reacting ketone with amine in the presence of Ti(IV)-isopropoxide and sodium cyanoborohydride in a solvent such as tetrahydrofuran(THF), methanol or ethanol, or a mixture of suitable alcohol and THF. The reaction temperature is about −78 to 100° C., and the reaction time is dozens of minutes to 2 days.

Method 2



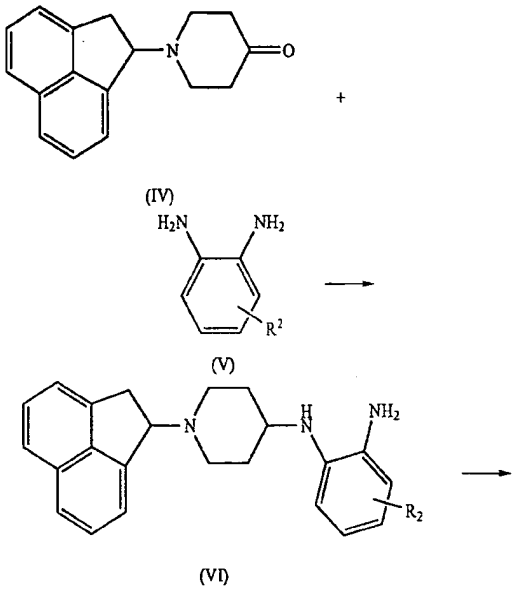
wherein each symbol is as defined above.

The compound of the formula (I-1) wherein R^1 is hydrogen, is subjected to alkylation, alkenylation, phenylation, benzylation or acylation to prepare a compound of the formula (I).

The compound of the formula (I-1) wherein R is hydrogen, can be subjected to alkylation, alkenylation, phenylation, benzylation or acylation according to a conventional method,

for example, in the presence of corresponding alkyl-halide, alkenyl-halide, benzyl-halide or acyl-halide such as methyl iodide, allyl bromide, benzyl bromide, ethyl bromide, acetyl chloride and ethyl bromoacetate. This reaction is carried out in the presence of metal hydride such as sodium hydride at a temperature of about −78 to 100° C. for a reaction time of dozens of minutes to 2 days.

Method 3



(IV) (V) (VI) (I-1)

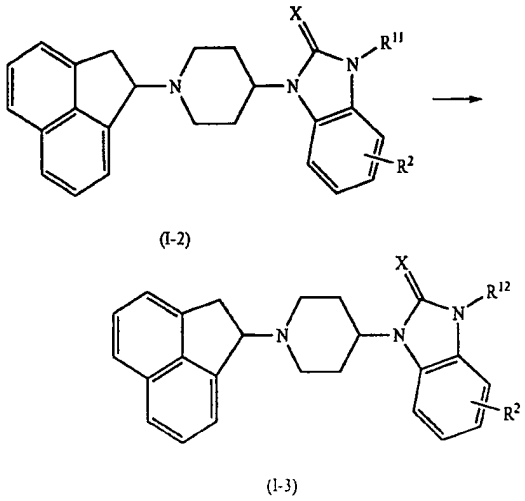
wherein each symbol is as defined above.

The compound of the formula (IV) is treated with phenylene diamine represented by the formula (V) to produce a compound of the formula (VI), which is cyclized to obtain a compound of the formula (I-1) wherein R^1 is hydrogen.

Reductive amination of a keto compound of the formula (IV) with phenylene diamine of the formula (V) is carried out in the presence of a metal hydride complex (for example, sodium triacetoxy borohydride, sodium cyanoborohydride, sodium borohydride, lithium borohydride and lithium aluminum hydride) in N,N-dimethylformamide, dimethylsulfoxide, pyridine, dioxane, tetrahydrofuran, acetonitrile, chloroform, methylene chloride, dichloroethane, methanol, ethanol, diethyl ether and the like, or a mixed solvent thereof. The reaction temperature is about −78 to 100° C., and the reaction time is dozens of minutes to 2 days. In addition, phenylene diamine of the formula (V) and the keto compound of the formula (IV) are known compounds. For example, phenylene diamine of the formula (V) can be prepared by the method described in J. Org. Chem., 2001, 66, 919 or in Org. Synth., 1943, 501, and the keto compound of the formula (IV) can be prepared by the method described in Bioorganic & Medicinal Chemistry Letters, 1999, 9, 2343.

The compound of the formula (VI) prepared in the present reaction can be carbonylated or thiocarbonylated by a known method (See, Bioorganic & Medicinal Chemistry Letters, 1996, 6, 1641, Chem. Pharm. Bull., 1989, 37, 962, Bioorganic & Medicinal Chemistry Letters, 1999, 9, 1537, etc.) to produce a compound of the formula (I-1).

Method 4



(I-2) (I-3)

wherein R^{11} is lower alkyl-carboxyl and R^{12} is lower alkyl-C(O)NR^3R^4. R^3, R^4 and X are as defined above.

A carbonic acid compound represented by the formula (I-2) or a reactive derivative thereof is reacted with amine to obtain a compound of the formula (I-3). The reactive derivative of a carbonic acid compound includes acid halide such as acid chloride, acid anhydride, mixed acid anhydride formed from ethyl chloroformate and the like, ester such as methyl ester and ethyl ester and a reactive derivative formed from carbodiimide such as WSC.HCl (water soluble carbodiimide hydrochloride) and DCC (dicyclohexyl carbodiimide), and the like. The reaction is carried out in an organic solvent such as N,N-dimethylformamide, dimethylsulfoxide, dioxane, tetrahydrofuran, acetonitrile, chloroform, methylene chloride, dichloroethane and toluene. The reaction temperature is about −78 to 100° C., and the reaction time is dozens of minutes to 2 days. Further, if necessary, an organic base such as pyridine, triethylamine and diisopropylethylamine is used as a deoxidizer.

Thus-synthesized compound of the formula (I) can be obtained as a racemate, and the racemic mixture can be converted to an enantiomer component thereof to produce an optically pure compound.

In addition, enantiomer of the compound of the formula (I) can be also produced by using optically active materials.

If necessary, the obtained compound of the formula (I) is converted to a pharmaceutically acceptable salt. The salt formation is per se known, and further carried out by well-known method at room temperature. A salt with an organic acid is also considered as well as salt with inorganic acid, and for a compound having a carboxyl group, salt with inorganic base is also considered. Examples of such salt are an acid-addition salt such as hydrochloride, oxalate and a fumarate, a sodium salt, a potassium salt, a calcium salt, a magnesium salt and the like.

The ORL-1 receptor agonist which is an active ingredient of a preventive and/or therapeutic agent for a sleep disorder of the present invention is not limited if it has agonistic activity for the ORL-1 receptor, but is preferably a compound having an affinity of 1000 nmol/L or less IC_{50} value for an ORL-1 receptor, and further inhibits cAMP elevation caused by a

cAMP inducer by 50% or more at a concentration of 1000 nmol/L or less. Examples of the cAMP inducer include forskolin and isoproterenol.

The compound having an agonistic activity for the ORL-1 receptor is preferably the compound of the formula (I), but also includes the compound having an agonistic activity for the ORL-1 receptor among the piperidine compounds or the amide compounds disclosed in publications such as JP-A-2000-26466, JP-A-11-228575, JP-A-10-212290, JP-A-2000-53686, WO00/14067, WO99/29696, EP1122257, JP-A-2001-39974, WO00/08013, WO99/36421, EP0997464, WO98/54168, WO00/31061, JP-A-2001-58991, WO01/39767, WO01/39775, WO02/085291, WO02/085354, WO02/085355, WO02/085361, WO00/27815, WO00/06545, WO99/59997, WO99/48492, WO02/26714 and WO03/000677. The "ORL-1 receptor agonist" in the present invention also includes ORL-1 receptor agonist compounds described in these publications.

Among these, specific examples are

(RS)-8-(acenaphthen-1-yl)-1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one,

8-(decahydro-naphthalen-2-yl)-3-methyl-1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one,

(1S,3aS)-8-(2,3,3a,4,5,6-hexahydro-1H-phenalene-1-yl)-1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one,

1-(1-cyclooctylmethyl-4-piperidinyl)-2-(4-methylpiperadinyl)-1H-benzoimidazole and the like though the chemical structure is not especially limited.

The effects of the present invention will be explained in detail in the section of pharmacological tests below. The present inventors have investigated at first if compounds having various chemical structures have an agonistic and/or antagonistic activity for the ORL-1 receptor, and then have administered compounds having an agonistic or antagonistic activity for the ORL-1 receptor to rats, and as results, they have found that a compound having an ORL-1 receptor agonistic activity also showed the phase advancing effect.

Since the present invention is characterized by the findings that an ORL-1 receptor agonist shows the phase advancing effect regardless of the chemical structure, the strength of their effects does not affect the usefulness of the present invention.

The sleep disorder which is the subject for the preventive and/or therapeutic agent of the present invention includes, for example, a circadian rhythm sleep disorder such as jet-lag syndromes, a shift-work sleep disorder, or delayed sleep phase syndromes. The circadian rhythm sleep disorder also includes the disorder peculiar to the elders (a geriatric circadian rhythm sleep disorder).

In addition, the preventive and/or therapeutic agent of the present invention can be used suitably for a bright light therapy.

A compound having an ORL-1 receptor agonistic activity (an ORL-1 receptor agonist) in the present invention can be administered orally or non-orally. Dosage form includes tablet, capsule, granule, powder, injection, ointment, and suppository and the like. These can be formulated by generally used techniques combining the ORL-1 receptor agonist and various pharmaceutically acceptable additives (an excipient, a diluent, a lubricant, a binder, a disintegrant, a coating agent, a filming agent, a base, a solvent, etc.). For example, an oral formulation such as a tablet, a capsule, a granule and a powder can be prepared using a diluent such as lactose, crystalline cellulose, starch and vegetable oil, a lubricant such as magnesium stearate and talc, a binder such as hydroxypropyl cellulose and polyvinyl pyrrolidone, a disintegrant such as carboxymethyl cellulose calcium and low-substituted hydroxypropylmethyl cellulose, a coating agent such as hydroxypropylmethylcellulose, macrogol and silicone resin, a filming agent such as gelatin film, as desired. An ointment can be prepared using a commonly used base such as white Vaseline and liquid paraffin.

The amount of an ORL-1 receptor agonist, an active ingredient in these formulations is 0.1 to 100% by weight, suitably 1 to 50% by weight. In addition, the dose may be suitably selected depending on symptoms, age, dosage form and the like. For the oral formulation, the dose is usually 0.1 to 5000 mg, preferably, 1 to 1000 mg per day and may be administered in a single dose or divided doses.

In addition, the present invention provides a commercial package comprising the above-described preventive and/or therapeutic agent containing an ORL-1 receptor agonist, and a document describing that the preventive and/or therapeutic agent can be or should be used for preventing and/or treating a sleep disorder.

The results of Examples, Formulation Examples and Pharmacological Examples are shown in the following. These are for better understanding of the present invention and do not limit the scope of the present invention.

EXAMPLE 1

(RS)-1-[1-(acenaphthen-1-yl)piperidin-4-yl]-1,3-dihydro-2H-benzoimidazol-2-one

(1) 1-Naphthylacetic acid (100 g, 530 mmol) was dissolved in dichloromethane (15 ml). Thionyl chloride (158 g, 1.32 mol) was added under ice-cooling and the mixture was heated under reflux for 1 hr. The solvent was evaporated and 1,2-dichloroethane (500 ml) was added to the obtained residue for dissolution. Aluminum chloride (150 g, 1.12 mol) was added under ice-cooling, and the mixture was stirred at room temperature for 1 hr. The reaction mixture was poured into ice water, and the mixture was extracted with dichloromethane. The extract was washed with water and saturated brine, dried over magnesium sulfate and concentrated to give acenaphthen-1-one (80 g) as yellow crystals.

^{1}H-NMR($CDCl_3$)δ_{TMS}: 3.79(s, 2H), 7.43(d, J=6.8 Hz, 1H), 7.57(t, J=6.8 Hz, 1H), 7.68(t, J=7.5 Hz, 1H), 7.79(d, J=6.8 Hz, 1H), 7.93(d, J=6.8 Hz, 1H), 8.06(d, J=6.8 Hz, 1H)

FAB-MS(M+H)$^+$: 169

(2) Acenaphthen-1-one (1.68 g, 10 mmol) was dissolved in tetrahydrofuran (THF, 15 ml). 4-(2-Keto-1-benzoimidazolinyl)piperidine (2.17 g, 10 mmol) and tetraisopropyl orthotitanate (3.4 g, 12 mmol) were added and the mixture was stirred at room temperature for 20 hr. The solvent was evaporated and a mixed solvent (15 ml) of THF/ethanol (1:2) was added to the obtained residue for dissolution. Sodium cyanoborohydrate (2.1 mmol) was added to this solution, and the mixture was stirred at stirred at room temperature for one day. Water was added, and the precipitate was removed by celite filtration and washed with ethanol. The filtrate was extracted with chloroform and washed with water and saturated brine. The extract was dried over sodium sulfate, and concentrated. The obtained residue was purified by silica gel column chromatography (chloroform/methanol) to give the title compound (0.68 g) as yellow crystals.

^{1}H-NMR($CDCl_3$)δ_{TMS}: 1.74-1.82(m, 2H), 2.36-2.60(m, 4H), 2.81(m, 1H), 3.01(m, 1H), 3.42(d, J=5.6 Hz, 2H), 4.29-4.36(m, 1H), 4.98(t, J=5.6 Hz, 1H), 7.01(m, 3H), 7.28-7.31 (m, 2H), 7.43-7.53(m, 3H), 7.60-7.62(m, 1H), 7.69(m, 1H), 9.77(brs, 1H)

FAB-MS(M+H)$^+$: 370

EXAMPLE 2

(RS)-1-[1-(acenaphthen-1-yl)piperidin-4-yl]-1,3-dihydro-5-fluoro-2H-benzoimidazol-2-one

The title compound was obtained as pale-yellow crystals according to Example 1 and using 4-(5-fluoro-2-keto-1-benzoimidazolinyl)piperidine.

^{1}H-NMR($CDCl_3$)δ_{TMS}: 1.72-1.85(m, 2H), 2.38-2.56(m, 4H), 2.86(m, 1H), 3.11(m, 1H), 3.42(d, J=5.6 Hz, 2H), 4.30-4.36(m, 1H), 4.98(t, J=5.6 Hz, 1H), 6.68(dd, J=13.2, 7.8 Hz, 1H), 7.28-7.31(m, 2H), 7.46-7.53(m, 3H), 7.60(d, J=7.8 Hz, 1H), 7.62(m, 1H), 7.69(m, 1H), 9.66(brs, 1H)

FAB-MS(M+H)$^+$: 388

EXAMPLE 3

(RS)-1-[1-(acenaphthen-1-yl)piperidin-4-yl]-1,3-dihydro-6-fluoro-2H-benzoimidazol-2-one

The title compound was obtained as pale-yellow crystals according to Example 1 and using 4-(6-fluoro-2-keto-1-benzoimidazolinyl)piperidine.

^{1}H-NMR($CDCl_3$)δ_{TMS}: 1.72-1.86(m, 2H), 2.36-2.54(m, 4H), 2.88(m, 1H), 3.11(m, 1H), 3.42(d, J=5.6 Hz, 2H), 4.32-4.38(m, 1H), 4.96(t, J=5.6 Hz, 1H), 6.72(dd, J=13.2, 7.8 Hz, 1H), 7.33-7.36(m, 2H), 7.46-7.53(m, 3H), 7.60(d, J=7.8 Hz, 1H), 7.62(m, 1H), 7.69(m, 1H), 9.78(brs, 1H)

FAB-MS(M+H)$^+$: 388

EXAMPLE 4

Ethyl (RS)-2-{3-[1-(acenaphthen-1-yl)piperidin-4-yl]-2,3-dihydro-2-oxo-benzoimidazol-1-yl}acetate

(RS)-1-[1-(Acenaphthen-1-yl)piperidin-4-yl]-1,3-dihydro-2H-benzoimidazol-2-one (1.5 g, 4 mmol) was dissolved in dimethylformamide (DMF, 15 ml). Sodium hydride (200 mg, 60%) was added and the suspension was stirred at 50° C. for 30 min. The mixture was cooled to room temperature, ethyl bromoacetate (0.75 g, 4.5 mmol) was added and the mixture was stirred for 1 hr. The reaction mixture was poured into water and the mixture was extracted with ethyl acetate. The extract was washed with water and saturated aqueous ammonium chloride solution, dried over magnesium sulfate, and concentrated. The obtained residue was purified by silica gel column chromatography (chloroform/methanol) to give the title compound (1.6 g) as pale-yellow crystals.

^{1}H-NMR($CDCl_3$)δ_{TMS}: 1.25(t, J=7.1, 3H), 1.82(m, 2H), 2.42-2.58(m, 4H), 2.78(m, 1H), 3.03((m, 1H), 3.44(m, 2H), 4.22(q, J=7.1 Hz, 2H), 4.35(m, 1H), 4.61(s, 2H), 5.01(m, 1H), 6.87(m, 1H), 7.05(m, 2H), 7.31(m, 2H), 7.45-7.55(m, 3H), 7.63(m, 1H), 7.71(m, 1H)

FAB-MS(M+H)$^+$: 456

EXAMPLE 5

(RS)-2-{3-[1-(acenaphthen-1-yl)piperidin-4-yl]-2,3-dihydro-2-oxo-benzoimidazol-1-yl}acetic Acid

Ethyl (RS)-2-{3-[1-(acenaphthen-1-yl)piperidin-4-yl]-2,3-dihydro-2-oxo-benzoimidazol-1-yl}acetate (1.6 g) was dissolved in ethanol (10 ml) and 2N-aqueous sodium hydroxide solution (10 ml) was added. The mixture was stirred at room temperature for 30 min. The reaction mixture was poured into water, thereto was added to 1N-hydrochloric acid for neutralization, and the mixture was extracted with chloroform. The extract was washed with water and saturated brine, dried over magnesium sulfate, and concentrated. The obtained solid was washed with ethyl acetate to give the title compound (1.3 g) as pale-yellow crystals.

^{1}H-NMR(DMSO-d_6)δ_{TMS}: 1.72-1.83(m, 2H), 2.63-3.12(m, 5H), 3.30(m, 1H), 3.50-3.70(m, 2H), 4.49(m, 1H), 4.58(s, 2H), 5.36(m, 1H), 7.02-7.13(m, 2H), 7.14(d, J=6.8 Hz, 1H), 7.40(d, J=6.8 Hz, 1H), 7.52-7.65(m, 3H), 7.72(d, J=8.3 Hz, 1H), 7.84(d, J=8.3 Hz, 1H), 8.31(m, 1H), 11.55(brs, 1H)

FAB-MS(M+H)$^+$: 428

EXAMPLE 6

(RS)-1-[1-(acenaphthen-1-yl)piperidin-4-yl]-3-(2-oxo-2-piperazin-1-ylethyl)-1,3-dihydro-2H-benzoimidazol-2-one dihydrochloride

(1) (RS)-2-{3-[1-(Acenaphthen-1-yl)piperidin-4-yl]-2,3-dihydro-2-oxo-benzoimidazol-1-yl}acetic acid (0.85 g, 2 mmol) was dissolved in DMF (10 ml). Boc-piperazine (tert-butoxycarbonylpiperazine) (0.37 g, 2 mmol), WSC.HCl (water soluble carbodiimide hydrochloric acid) (0.46 g, 2.4 mmol), HOBt (hydroxybenzotriazole) (0.37 g, 2.4 mmol) and triethylamine (0.53 ml, 3.8 mmol) were added and the mixture was stirred at room temperature for 10 hr. The reaction mixture was poured into water, and the mixture was extracted with ethyl acetate. The extract was washed with water and saturated aqueous ammonium chloride solution, dried over magnesium sulfate, and concentrated. The obtained residue was purified by silica gel column chromatography (chloroform/methanol) to give a yellow solid (0.8 g).

(2) The above-mentioned yellow solid (0.8 g) was dissolved in 4N-hydrochloric acid/dioxane (10 ml) and the mixture was stirred at room temperature for 1 hr. The solvent was evaporated and isopropyl ether was added to the residue. The obtained crystals were collected by filtration to give the title compound (0.5 g) as yellow crystals.

^{1}H-NMR(DMSO-d_6)δ_{TMS}: 1.76-1.88(m, 2H), 3.11-3.82(m, 15H), 3.96(m, 1H), 4.71(m, 1H), 4.83(s, 2H), 5.63(m, 1H), 7.02-7.12(m, 3H), 7.46(d, J=6.8 Hz, 1H), 7.58(t, J=8.0 Hz, 1H), 7.67(t, J=7.8 Hz, 1H), 7.76-7.84(m, 2H), 7.92(m, 1H), 8.25(d, J=7.8 Hz, 1H), 9.42(brs, 2H), 12.20(brs, 1H)

FAB-MS(M+H)$^+$: 496

EXAMPLE 7

(RS)-1-[1-(acenaphthen-1-yl)piperidin-4-yl]-3-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-1,3-dihydro-2H-benzoimidazol-2-one dihydrochloride

(RS)-2-{3-[1-(Acenaphthen-1-yl)piperidin-4-yl]-2,3-dihydro-2-oxo-benzoimidazol-1-yl}acetic acid (0.85 g, 2 mmol) was dissolved in DMF (10 ml). 1-Methylpiperazine (0.2 g, 2 mmol), WSC.HCl (0.46 g, 2.4 mmol), HOBt (0.37 g, 2.4 mmol) and triethylamine (0.53 ml, 3.8 mmol) were added and the mixture was stirred at room temperature for 8 hr. The reaction mixture was poured into water, and the mixture was extracted with ethyl acetate. The extract was washed with water and saturated aqueous ammonium chloride solution, dried over magnesium sulfate, and concentrated. The obtained residue was purified by silica gel column chromatography (chloroform/methanol) and hydrochloric acid/ethanol was added to give the title compound (0.73 g) as a yellow solid.

^{1}H-NMR(DMSO-d_6)δ_{TMS}: 1.76-1.89(m, 2H), 2.77-3.74(m, 16H), 3.96(m, 1H), 4.16(m, 1H), 4.31(m, 1H), 4.71(m,

1H), 4.76(d, J=17.3 Hz, 1H), 4.92(d, J=17.3 Hz, 1H), 5.63(m, 1H), 7.02-7.09(m, 3H), 7.45-7.55(m, 1H), 7.56-7.65(m, 1H), 7.67-7.69(m, 1H), 7.76-7.82(m, 2H), 7.91-7.94(m, 1H), 8.25 (m, 1H), 11.32(brs, 1H), 12.23(brs, 1H)

FAB-MS(M+H)$^+$: 510

EXAMPLE 8

(RS)-1-[1-(acenaphthen-1-yl)piperidin-4-yl]-3-(2-morpholin-4-yl-2-oxoethyl)-1,3-dihydro-2H-benzoimidazol-2-one hydrochloride

The title compound was obtained as pale-yellow crystals according to Example 7 and using morpholine.

^{1}H-NMR(DMSO-d_6)δ_{TMS}: 1.78-1.89(m, 2H), 2.83(m, 1H), 3.05(m, 2H), 3.31-3.76(m, 12H), 3.95(m, 1H), 4.69(m, 1H), 4.76(s, 2H), 5.63(m, 1H), 7.02-7.08(m, 3H), 7.45-7.47 (m, 1H), 7.56-7.60(m, 1H), 7.66-7.78(m, 3H), 7.92-7.94(m, 1H), 8.18(m, 1H), 11.85(brs, 1H)

FAB-MS(M+H)$^+$: 497

EXAMPLE 9

(RS)-1-[1-(acenaphthen-1-yl)piperidin-4-yl]-1,3-dihydro-2H-benzoimidazole-2-thione

(1) Acenaphthen-1-one (34 g, 200 mmol) was dissolved in methanol (300 ml). Sodium borohydride (8 g, 200 mmol) was added to this solution under ice-cooling, and the mixture was stirred at room temperature for 1 hr. The reaction mixture was poured into water, and the mixture was extracted with ethyl acetate. The extract was washed with water and saturated brine, dried over magnesium sulfate, and concentrated to give 1-acenaphthenol (33 g) as yellow crystals.

(2) To a solution of 1-acenaphthenol (33 g, 190 mmol) and diphenylphosphorylazide (63 g, 230 mmol) in toluene (300 ml) was cooled to 0° C., DBU (diazabicycloundecene) (35 g, 230 mmol) was added and the mixture was stirred at room temperature for 6 hr. The reaction mixture was poured into water and extracted with toluene. The combined organic phase was washed with water, dried over magnesium sulfate, and concentrated. A crude product was dissolved in a mixed solvent (330 ml) of THF/water (10:1), triphenylphosphine (53 g) was added thereto, and the mixture was heated under reflux for 6 hr. After cooling to room temperature, the solvent was evaporated and 1N-hydrochloric acid (200 ml) was added to the residue. Unnecessary materials were extracted with ethyl acetate. The aqueous phase was alkalified with potassium carbonate and extracted with chloroform. The extract was washed with water and saturated brine, dried over magnesium sulfate, and concentrated to give acenaphthen-1-yl-amine (20 g) as a red oil.

(3) Acenaphthen-1-yl-amine (20 g, 118 mmol) was dissolved in ethanol (200 ml). Potassium carbonate (1.7 g, 12 mmol) and 1-ethyl-1-methyl-4-oxopiperidinium iodide (38 g) dissolved in water (100 ml) was added and the mixture was heated under reflux for 1 hr. The reaction mixture was poured into water, and the mixture was extracted with ethyl acetate. The extract was washed with water and saturated brine, dried over magnesium sulfate, and concentrated. The obtained residue was purified by silica gel column chromatography (chloroform/methanol) to give 1-(acenaphthen-1-yl)-piperidin-4-one (23 g) as yellow crystals.

(4) To a solution of 1-(acenaphthen-1-yl)-piperidin-4-one (12 g, 48 mmol) and 1,2-phenylenediamine (10.8 g, 100 mmol) in THF (100 ml) was cooled to 0° C. were added sodium triacetoxy borohydride (34 g) and acetic acid (12 ml) and the mixture was stirred at room temperature for 17 hr. The reaction mixture was poured into water and potassium carbonate was added for neutralization. The mixture was extracted with ethyl acetate. The extract was washed with water and saturated brine, dried over sodium sulfate, and concentrated. The obtained residue was purified by silica gel column chromatography (chloroform/methanol) to give N-[1-(acenaphthen-1-yl)piperidin-4-yl]-benzene-1,2-diamine (8.5 g) as yellow crystals.

(5) N-[1-(Acenaphthen-1-yl)piperidin-4-yl]-benzene-1,2-diamine (1 g, 3 mmol) was dissolved in THF (30 ml), and triethylamine (1.4 ml, 10 mmol) and 1,1'-thiocarbonyldiimidazole (0.63 g, 3.5 mmol) were added. The mixture was stirred at room temperature for 3 hr. The reaction mixture was poured into water, and the mixture was extracted with ethyl acetate. The extract was washed with water and saturated aqueous ammonium chloride solution, dried over magnesium sulfate, and concentrated. The obtained residue was purified by silica gel column chromatography (chloroform/methanol) to give the title compound (1.17 g) as a gray-white solid.

^{1}H-NMR($CDCl_3$)δ_{TMS}: 1.85(m, 2H), 2.42-2.55(m, 3H), 2.63(m, 1H), 2.82(m, 1H), 3.04(m, 1H), 3.44(d, J=5.6 Hz, 2H), 4.98(t, J=5.6 Hz, 1H), 5.19(m, 1H), 7.15-7.24(m, 3H), 7.29(m, 1H), 7.45(m, 1H), 7.50-7.63(m, 4H), 7.68(m, 1H), 9.62(brs, 1H)

FAB-MS(M+H)$^+$: 386

EXAMPLE 10

(RS)-1-[1-(acenaphthen-1-yl)piperidin-4-yl]-1,3-dihydro-3-methyl-2H-benzoimidazole-2-thione

(RS)-1-[1-(Acenaphthen-1-yl)piperidin-4-yl]-1,3-dihydro-2H-benzoimidazole-2-thione (1 g, 2.6 mmol) was dissolved in DMF (15 ml) and sodium hydride (120 mg, 60%) was added. The suspension was stirred at 50° C. for 30 min. After cooling to room temperature, methyl iodide (0.4 g, 2.8 mmol) was added and the mixture was stirred for 1 hr. The reaction mixture was poured into water, and the mixture was extracted with ethyl acetate. The extract was washed with water and saturated aqueous ammonium chloride solution, dried over magnesium sulfate, and concentrated. The obtained residue was purified by silica gel column chromatography (chloroform/methanol) to give the title compound (1.05 g) as pale-yellow crystals.

^{1}H-NMR($CDCl_3$)δ_{TMS}: 1.83(m, 2H), 2.38(m, 1H), 2.51-2.64(m, 3H), 2.78(s, 3H), 2.83(m, 1H), 3.05(m, 1H), 3.45(d, J=5.6 Hz, 2H), 4.15(m, 1H), 5.01(t, J=5.6 Hz, 1H), 7.15-7.21 (m, 2H), 7.31(m, 1H), 7.47(m, 1H), 7.54-7.73(m, 6H)

FAB-MS(M+H)$^+$: 400

EXAMPLE 11

(R)-1-[1-(acenaphthen-1-yl)piperidin-4-yl]-1,3-dihydro-2H-benzoimidazol-2-one

(1) (R)-2-Methyl-CBS-oxazaboro-lidine (50 ml, 1 mol toluene solution) was cooled to −30° C., and a borane.THF complex (250 ml, 1 mol THF solution) was added. The mixture was stirred for 45 min. Acenaphthen-1-one (40 g, 240 mmol) was dissolved in dichloromethane (500 ml) and the solution was added dropwise. The mixture was stirred

under cooling (−30° C.) for 2 hr. Then, methanol (80 ml) and 1N-hydrochloric acid (100 ml) were added under ice-cooling, and the mixture was extracted with ethyl acetate. The extract was washed with water and saturated aqueous ammonium chloride solution, dried over magnesium sulfate, and concentrated to give (S)-1-acenaphthenol (35 g) as pale-yellow crystals.

^{1}H-NMR($CDCl_3$)δ_{TMS}: 1.96(brs, 1H), 3.24(d, J=17.5 Hz, 1H), 3.80(dd, J=17.5, 7.5 Hz, 1H), 5.73(m, 1H), 7.30(d, J=6.8 Hz, 1H), 7.48(t, J=6.8 Hz, 1H), 7.53-7.56(m, 2H), 7.64(d, J=7.5 Hz, 1H), 7.75(m, 1H)

FAB-MS(M+H)$^+$: 171

$[\alpha]_D^{20}$=1.93

(2) A solution of (S)-1-acenaphthenol (35 g, 200 mmol) and diphenylphosphorylazide (66 g, 240 mmol) in toluene (300 ml) was cooled to 0° C. and DBU (36 g, 240 mmol) was added. The mixture was stirred at room temperature for 6 hr. The reaction mixture was poured into water, and extracted with toluene. The combined organic phase was washed with water, dried over magnesium sulfate, and concentrated. The crude product was dissolved in a mixed solvent (220 ml) of THF/water (10:1) and triphenylphosphine (40 g) was added. The mixture was heated under reflux for 6 hr. After cooling to room temperature, the solvent was evaporated and 1N-hydrochloric acid (200 ml) was added to the residue. Unnecessary materials were removed by extraction with ethyl acetate. The aqueous phase was alkalified with potassium carbonate and extracted with chloroform. The extract was washed with water and saturated brine, dried over magnesium sulfate, and concentrated. Hydrochloric acid/ethanol was added to the obtained red oil to give (R)-acenaphthen-1-yl-amine hydrochloride (25 g) as yellow crystals.

^{1}H-NMR(DMSO-d_6)δ_{TMS}: 3.32(d, J=17.3 Hz, 1H), 3.82 (dd, J=17.3, 8.1 Hz, 1H), 5.20(m, 1H), 7.40(d, J=6.8 Hz, 1H), 7.48(t, J=6.8 Hz, 1H), 7.55-7.62(m, 2H), 7.73(d, J=8.1 Hz, 1H), 7.85(d, J=7.8 Hz, 1H), 8.9(brs, 3H)

FAB-MS(M+H)$^+$: 170

(3) (R)-Acenaphthen-1-yl-amine.hydrochloride (25 g) was dissolved in water (200 ml) and the mixture was alkalified with potassium carbonate and extracted with chloroform. The extract was washed with water and saturated brine, dried over magnesium sulfate, and concentrated. The obtained (R)-acenaphthen-1-yl-amine (21 g, 124 mmol) was dissolved in ethanol (200 ml). Potassium carbonate (2.5 g, 18 mmol) and 1-ethyl-1-methyl-4-oxopiperidinium iodide (40 g) dissolved in water (100 ml) was added and the mixture was heated under reflux for 2 hr. The reaction mixture was poured into water, and the mixture was extracted with ethyl acetate. The extract was washed with water and saturated brine, dried over magnesium sulfate, and concentrated. The obtained residue was purified by silica gel column chromatography (chloroform/methanol) to give (R)-1-(acenaphthen-1-yl)-piperidin-4-one (22 g) as a red-yellow oil.

(4) A solution of (R)-1-(acenaphthen-1-yl)-piperidin-4-one (12.6 g, 50 mmol) and 1,2-phenylenediamine (10.8 g, 100 mmol) in THF (100 ml) was cooled to (0° C.), sodium triacetoxy borohydride (30 g) and acetic acid (12 ml) were added thereto, and the mixture was stirred at room temperature for 24 hr. The reaction mixture was poured into water, and potassium carbonate was added for neutralization. The mixture was extracted with ethyl acetate. The extract was washed with water and saturated brine, dried over sodium sulfate, and concentrated. The obtained residue was purified by silica gel column chromatography (chloroform/methanol) to give (R)-N-[1-(acenaphthen-1-yl)piperidin-4-yl]-benzene-1,2-diamine (9 g) as yellow crystals.

(5) (R)-N-[1-(Acenaphthen-1-yl)piperidin-4-yl]-benzene-1,2-diamine (9 g, 26 mmol) was dissolved in THF (100 ml), and carbonyldiimidazole (5 g, 30 mmol) was added. The mixture was stirred at room temperature for 2 hr. The reaction mixture was poured into water, and the mixture was extracted with ethyl acetate. The extract was washed with water and saturated aqueous ammonium chloride solution, dried over magnesium sulfate, and concentrated. The obtained residue was purified by silica gel column chromatography (chloroform/methanol) to give the title compound (8.8 g) as a white solid.

^{1}H-NMR($CDCl_3$)δ_{TMS}: 1.74-1.82(m, 2H), 2.36-2.60(m, 4H), 2.81(m, 1H), 3.01(m, 1H), 3.42(d, J=5.6 Hz, 2H), 4.29-4.36(m, 1H), 4.98(t, J=5.6 Hz, 1H), 7.01(m, 3H), 7.28-7.31 (m, 2H), 7.43-7.53(m, 3H), 7.60-7.62(m, 1H), 7.69(m, 1H), 9.56(brs, 1H)

FAB-MS(M+H)$^+$: 370

$[\alpha]_D^{20}$=52.5°

EXAMPLE 12

(S)-1-[1-(acenaphthen-1-yl)piperidin-4-yl]-1,3-dihydro-2H-benzoimidazol-2-one

The title compound was obtained as white crystals according to Example 11 and using (S)-2-methyl-CBS-oxazaborolidine (1 mol toluene solution).

^{1}H-NMR($CDCl_3$)δ_{TMS}: 1.74-1.82(m, 2H), 2.36-2.60(m, 4H), 2.81(m, 1H), 3.01(m, 1H), 3.42(d, J=5.6 Hz, 2H), 4.29-4.36(m, 1H), 4.98(t, J=5.6 Hz, 1H), 7.01(m, 3H), 7.28-7.31 (m, 2H), 7.43-7.53(m, 3H), 7.60-7.62(m, 1H), 7.69(m, 1H), 9.67(brs, 1H)

FAB-MS(M+H)$^+$: 370

$[\alpha]_D^{20}$=−52.6°

EXAMPLE 13

(R)-3-acetyl-1-[1-(acenaphthen-1-yl)piperidin-4-yl]-1,3-dihydro-2H-benzoimidazol-2-one

(R)-1-[1-(Acenaphthen-1-yl)piperidin-4-yl]-1,3-dihydro-2H-benzoimidazol-2-one (6.2 g, 16.8 mmol) was dissolved in DMF (60 ml). Sodium hydride (0.9 g, 60%) was added and the suspension was stirred at 50° C. for 30 min. It was cooled to room temperature and acetyl chloride (1.5 g, 19 mmol) was added and the mixture was stirred for 3 hr. The reaction mixture was poured into water and the mixture was extracted with ethyl acetate. The extract was washed with water and saturated aqueous ammonium chloride solution, dried over magnesium sulfate, and concentrated. The obtained residue was purified by silica gel column chromatography (chloroform/methanol) to give the title compound (6.3 g) as pale-yellow crystals

^{1}H-NMR($CDCl_3$)δ_{TMS}: 1.68-1.81(m, 2H), 2.40-2.56(m, 4H), 2.74(s, 3H), 2.78(m, 1H), 3.02(m, 1H), 3.42(m, 2H), 4.30(m, 1H), 4.98(m, 1H), 7.11-7.31(m, 4H), 7.45-7.71(m, 5H), 8.24(m, 1H)

FAB-MS(M+H)$^+$: 412

$[\alpha]_D^{20}$=40.1°

EXAMPLE 14

(R)-1-[1-(acenaphthen-1-yl)piperidin-4-yl]-3-methanesulfonyl-1,3-dihydro-2H-benzoimidazol-2-one

The title compound was obtained as pale-yellow crystals according to Example 13 and using methanesulfonyl chloride.

^{1}H-NMR($CDCl_3$)δ_{TMS}: 1.71-1.85(m, 2H), 2.40-2.58(m, 4H), 2.85(s, 3H), 2.75(m, 1H), 3.02(m, 1H), 3.45(m, 2H), 4.28(m, 1H), 5.01(m, 1H), 7.1-7.31(m, 4H), 7.46-7.68(m, 5H), 8.28(m, 1H)

FAB-MS(M+H)$^+$: 448

$[\alpha]_D^{20}$=43.8°

EXAMPLE 15

Ethyl (R)-2-{3-[1-(acenaphthen-1-yl)piperidin-4-yl]-2,3-dihydro-2-oxo-benzoimidazol-1-yl}acetate

(R)-1-[1-(Acenaphthen-1-yl)piperidin-4-yl]-1,3-dihydro-2H-benzoimidazol-2-one (2.3 g, 6 mmol) was dissolved in DMF (20 ml) and sodium hydride (300 mg, 60%) was added. The suspension was stirred at 50° C. for 30 min. After cooling to room temperature, ethyl bromoacetate (1.17 g, 7 mmol) was added and the mixture was stirred for 2 hr. The reaction mixture was poured into water, and the mixture was extracted with ethyl acetate. The extract was washed with water and saturated aqueous ammonium chloride solution, dried over magnesium sulfate, and concentrated. The obtained residue was purified by silica gel column chromatography (chloroform/methanol) to give the title compound (2.6 g) as pale-yellow crystals.

^{1}H-NMR($CDCl_3$)δ_{TMS}: 1.26(t, J=7.1, 3H), 1.82(m, 2H), 2.40-2.56(m, 4H), 2.78(m, 1H), 3.01((m, 1H), 3.44(m, 2H), 4.21(q, J=7.1 Hz, 2H), 4.35(m, 1H), 4.61(s, 2H), 4.99(m, 1H), 6.87(m, 1H), 7.07(m, 2H), 7.31(m, 2H), 7.45-7.55(m, 3H), 7.63(m, 1H), 7.71(m, 1H)

FAB-MS(M+H)$^+$: 456

$[\alpha]_D^{20}$=40.2°

EXAMPLE 16

(R)-2-{3-[1-(acenaphthen-1-yl)piperidin-4-yl]-2,3-dihydro-2-oxo-benzoimidazol-1-yl}acetic acid

Ethyl (R)-2-{3-[1-(acenaphthen-1-yl)piperidin-4-yl]-2,3-dihydro-2-oxo-benzoimidazol-1-yl}acetate (2.6 g, 5.8 mmol) was dissolved in ethanol (10 ml), 2N-aqueous sodium hydroxide solution (10 ml) was added and the mixture was stirred at room temperature for 2 hr. The reaction mixture was poured into water, 1N-hydrochloric acid was added for neutralization, and the mixture was extracted with chloroform. The extract was washed with water and saturated brine, dried over magnesium sulfate, and concentrated. The obtained solid was washed with ethyl acetate to give the title compound (2.4 g) as pale-yellow crystals.

^{1}H-NMR(DMSO-d_6)δ_{TMS}: 1.71-1.83(m, 2H), 2.63-3.10 (m, 5H), 3.30(m, 1H), 3.58-3.70(m, 2H), 4.49(m, 1H), 4.58(s, 2H), 5.36(m, 1H), 7.02-7.13(m, 2H), 7.14(d, J=6.8 Hz, 1H), 7.40(d, J=6.8 Hz, 1H), 7.52-7.65(m, 3H), 7.72(d, J=8.3 Hz, 1H), 7.84(d, J=8.3 Hz, 1H), 8.31(m, 1H), 12.08(brs, 1H)

FAB-MS (M+H)$^+$: 428

$[\alpha]_D^{20}$=42.5°

EXAMPLE 17

(R)-1-[1-(acenaphthen-1-yl)piperidin-4-yl]-3-(2-oxo-2-piperazin-1-ylethyl)-1,3-dihydro-2H-benzoimidazol-2-one dihydrochloride

(1) (R)-2-{3-[1-(Acenaphthen-1-yl)piperidin-4-yl]-2,3-dihydro-2-oxo-benzoimidazol-1-yl}acetic acid (1.28 g, 3 mmol) was dissolved in DMF (15 ml). Boc-piperazine (0.56 g, 3 mmol), WSC.HCl (0.7 g, 3.6 mmol), HOBt (0.55 g, 2.4 mmol) and triethylamine (0.8 ml, 5.7 mmol) were added and the mixture was stirred at room temperature for 10 hr. The reaction mixture was poured into water, and the mixture was extracted with ethyl acetate. The extract was washed with water and saturated aqueous ammonium chloride solution, dried over magnesium sulfate, and concentrated. The obtained residue was purified by silica gel column chromatography (chloroform/methanol) to give a yellow solid (1.2 g).

(2) The above-mentioned compound was dissolved in 4N-hydrochloric acid/dioxane (10 ml) and the mixture was stirred at room temperature for 2 hr. The solvent was evaporated and isopropyl ether was added to the residue. The obtained crystals were collected by filtration to give the title compound (0.8 g) as yellow crystals.

^{1}H-NMR(DMSO-d_6)δ_{TMS}: 1.76-1.88(m, 2H), 3.11-3.82 (m, 15H), 3.96(m, 1H), 4.71(m, 1H), 4.83(s, 2H), 5.63(m, 1H), 7.02-7.12(m, 3H), 7.46(d, J=6.8 Hz, 1H), 7.58(t, J=8.0 Hz, 1H), 7.67(t, J=7.8 Hz, 1H), 7.76-7.84(m, 2H), 7.92(m, 1H), 8.25(d, J=7.8 Hz, 1H), 9.58(brs, 2H), 12.28(brs, 1H)

FAB-MS(M+H)$^+$: 496

$[\alpha]_D^{20}$=48.5°

EXAMPLE 18

(R)-2-{3-[1-(acenaphthen-1-yl)piperidin-4-yl]-2,3-dihydro-2-oxo-benzoimidazol-1-yl}-N-methylacetamide

(R)-2-{3-[1-(Acenaphthen-1-yl)piperidin-4-yl]-2,3-dihydro-2-oxo-benzoimidazol-1-yl}acetic acid (1 g, 2.3 mmol) was dissolved in DMF (10 ml). Methylamine hydrochloride (0.17 g, 2.5 mmol), WSC.HCl (0.53 g, 2.7 mmol), HOBt (0.43 g, 2.8 mmol) and triethylamine (0.7 ml, 5 mmol) were added and the mixture was stirred at room temperature for 15 hr. The reaction mixture was poured into water, and the mixture was extracted with ethyl acetate. The extract was washed with water and saturated aqueous ammonium chloride solution, dried over magnesium sulfate, and concentrated. The obtained residue was purified by silica gel column chromatography (chloroform/methanol) to give the title compound (0.7 g) as pale-yellow crystals.

^{1}H-NMR(DMSO-d_6)δ_{TMS}: 1.59-1.70(m, 2H), 2.28-2.49 (m, 4H), 2.58(s, 3H), 2.95(m, 1H), 3.35-3.43(m, 3H), 4.16(m, 1H), 4.40(s, 2H), 4.96(m, 1H), 7.02(m, 3H), 7.28-7.33(m, 1H), 7.45-7.57(m, 3H), 7.65(d, J=8.3 Hz, 1H), 7.72(d, J=7.8 Hz, 1H), 8.08(m, 1H)

FAB-MS(M+H)$^+$: 441

$[\alpha]_D^{20}$=43.2°

EXAMPLE 19

(R)-2-{3-[1-(acenaphthen-1-yl)piperidin-4-yl]-2,3-dihydro-2-oxo-benzoimidazol-1-yl}-N,N-dimethylacetamide

The title compound was obtained as pale-yellow crystals according to Example 18 and using dimethylamine hydrochloride.

1.76-^{1}H-NMR($CDCl_3$)δ_{TMS}: 1.84(m, 2H), 2.40-2.55(m, 4H), 2.78(m, 1H), 2.96(s, 3H), 3.01(m, 1H), 3.12(s, 3H), 3.45(m, 2H), 4.35(m, 1H), 4.66(s, 2H), 5.00(m, 1H), 6.99-7.07(m, 3H), 7.30(m, 2H), 7.45-7.70(m, 5H)

FAB-MS$(M+H)^+$: 455

$[\alpha]_D^{20}$=39.7°

EXAMPLE 20

(R)-2-{3-[1-(acenaphthen-1-yl)piperidin-4-yl]-2,3-dihydro-2-oxo-benzoimidazol-1-yl}acetamide

(R)-2-{3-[1-(Acenaphthen-1-yl)piperidin-4-yl]-2,3-dihydro-2-oxo-benzoimidazol-1-yl}acetic acid (400 mg, 0.9 mmol) was dissolved in dichloromethane (10 ml). Thionyl chloride (0.2 ml, 2.7 mmol) was added under ice-cooling, and the mixture was stirred at room temperature for 2 hr. The solvent was evaporated and aqueous ammonia (5 ml) was added to the obtained residue under ice-cooling, and the mixture was further stirred under ice-cooling. The precipitated crystals were collected by filtration to give the title compound (0.22 g) as pale-yellow crystals.

^{1}H-NMR(DMSO-d_6)δ_{TMS}: 1.62-1.70(m, 2H), 2.31-2.51 (m, 4H), 2.61(m, 1H), 2.97(m, 1H), 3.38(m, 2H), 4.18(m, 1H), 4.39(s, 2H), 4.97(m, 1H), 7.00-7.05(m, 3H), 7.22-7.33 (m, 3H), 7.45-7.73(m, 6H)

FAB-MS $(M+H)^+$: 427

$[\alpha]_D^{20}$=45°

FORMULATION EXAMPLE 1

Tablet

compound of the present invention	10.0 mg
lactose	50.0 mg
corn starch	20.0 mg
crystalline cellulose	29.7 mg
polyvinylpyrrolidone K30	5.0 mg
talc	5.0 mg
magnesium stearate	0.3 mg
	120.0 mg

The compound of the present invention, lactose, corn starch and crystalline cellulose were mixed, kneaded with polyvinylpyrrolidone K30 paste solution, and granulated by passing a 20 mesh sieve. After drying at 50° C. for 2 hr, the granules were passed through a 24 mesh sieve, talc and magnesium stearate were admixed and tablets (120 mg per tablet) were produced using a pounder having a diameter of 7 mm.

FORMULATION EXAMPLE 2

Capsule

compound of the present invention	10.0 mg
lactose	70.0 mg
corn starch	35.0 mg
polyvinylpyrrolidone K30	2.0 mg
talc	2.7 mg
magnesium stearate	0.3 mg
	120.0 mg

The compound of the present invention, lactose, corn starch and crystalline cellulose were mixed, kneaded with polyvinylpyrrolidone K30 paste solution, and granulated by passing a 20 mesh sieve. After drying at 50° C. for 2 hr, the granules were passed through a 24 mesh sieve, admixed with talc and magnesium stearate and the mixture was filled in a hard capsule (No. 4) to give capsules (120 mg).

The test results in the following shows that the ORL-1 receptor agonist is useful for preventing and/or treating a sleep disorder, for example, a circadian rhythm sleep disorder such as jet-lag syndromes, a shift-work sleep disorder or delayed sleep phase syndromes.

Hereinbelow, pharmacological actions of the medicament of the present invention will be explained by Experimental Examples.

As the test compounds, the following 4 kinds of compounds were used.

compound A: (RS)-8-(acenaphthen-1-yl)-1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one (synthesized according to the method described in Bioorganic & Medicinal Chemistry Letters, 1999, 9, 2343)

compound B: (R)-1-[1-(acenaphthen-1-yl)piperidin-4-yl]-1,3-dihydro-2H-benzoimidazol-2-one (compound of Example 11)

compound C: (R)-2-{3-[1-(acenaphthen-1-yl)piperidin-4-yl]-2,3-dihydro-2-oxo-benzoimidazol-1-yl}-N-methylacetamide (compound of Example 18)

compound D: N-(4-amino-2-methylquinolin-6-yl)-2-(4-ethylphenoxymethyl)benzamide hydrochloride (synthesized according to the method described in JTC-801, J. Med. Chem. 2000, 43, 4667)

EXPERIMENTAL EXAMPLE 1

ORL-1 Receptor Binding Test

Experimental Method and Measurement

Binding test of [^{3}H]-nociceptin was carried out using a standard product of the receptor prepared from cerebral cortex of rat. Specifically, 50 μl of a test substance solution of each concentration, 900 μl of a solution of the receptor standard product, and 50 μl of a labeled ligand [^{3}H]-nociceptin were added to a polypropylene tube successively, and were subjected to reaction at 25° C. for 20 minutes. The reaction solution was sucking-filtered with Whatman GF/B, glass filter in a cell harvester. The filter was three times washed with an ice-cooled, 50 mmol/l Tris/chloric acid buffer solution, and put into a measurement vial. ACS-II (2 ml, Amersham Pharmacia Biotech), liquid scintillation cocktail was added,

and then the radioactivity was measured using a liquid scintillation counter (LSC-5100, ALOKA CO., LTD.). A non-labeled ligand test compound A was used to obtain the amount of non-specific binding. Binding inhibition (%) and inhibition constant (Ki value) were calculated according to the following calculation formulae.

$$\text{Binding inhibition (\%)} = \{1-(B-N)/(T-N)\} \times 100$$

N: Amount of non-specific binding, T: Amount of total binding, B: Amount of binding in the presence of test substance

$$\text{Inhibition constant } (Ki \text{ value}) = IC_{50}/(1+L/Kd)$$

IC_{50}: 50% Inhibition concentration, L: Concentration of a labeled ligand, Kd: Dissociation constant of a labeled ligand

Results and Discussion

As shown in FIG. **1**, test compounds A, B, C and D inhibited the binding of [^{3}H]-nociceptin, depending on a concentration, and the IC_{50} values were 84.2, 72.8, 4.4, 500 nmol/L, respectively. In addition, Ki values were 10.0, 8.4, 0.51 and 60.6 nmol/L, respectively.

From the above results, it was obvious that any one of test compounds A, B, C and D had affinity for an ORL-1 receptor.

EXPERIMENTAL EXAMPLE 2

Agonist Action

Experimental Method and Measurement

ORL-1 receptor agonistic activity was measured using HEK293 cells which strongly expressed a human ORL-1 receptor by the index of inhibiting activity for cAMP elevation by forskolin stimulation. In other words, cells expressing a human ORL-1 receptor was incubated overnight using a collagen-coated 96-well microplate, the incubation solution was discarded, and 100 μl of a Krebs-Ringer solution was added. Then, 50 μl of a test substance solution of each concentration was added, and was pre-incubated at 37° C. for 5 minutes. Further, 50 μl of a forskolin solution (1 μmol/L of a final concentration) was added and incubated at 37° C. for 15 minutes. After discarding the supernatant, 200 μl of a cell solubilizer was added to obtain a sample for cAMP assay in cells. cAMP concentration in the sample for cAMP assay was measured with BIOTRAK (Amersham Pharmacia Biotech), a kit for cAMP assay.

Results and Discussion

As shown in FIG. **2**, the test compounds A, B and C inhibited cAMP production depending on concentration. Therefore, it was obvious that the test compounds A, B and C had ORL-1 receptor agonistic activity. On the other hand, the test compound D did not inhibit cAMP production though it showed affinity for an ORL-1 receptor. In other words, it was obvious that the test compound D was ORL-1 receptor antagonist.

EXPERIMENTAL EXAMPLE 3

Phase Shift of Circadian Rhythm by the ORL-1 Receptor Agonist Under a Constant Dark Condition

Experimental Method and Measurement

The rats which had been previously subject to surgery to implant transmitter for measuring body temperature and activity (TA10TA-F20) in the peritoneal cavity, was used in this experiment. After a certain recovery period, the rats were put into a soundproof box having equipped with a signal-receiving board, and were raised individually under a constant dark condition. The body temperature and the activity of rats were measured automatically with a telemetry auto-measuring system every 5 minutes, and the results of the measurement were stored in a computer. The body-temperature rhythm was indicated by plotting time in horizontal axis, and days in vertical axis and temperatures higher than a mean body-temperature calculated by a least squares method were represented in a black line. After confirming that the body-temperature rhythm was recorded to be stable for 10 days or longer for a constant period, the ORL-1 receptor agonist was administered intraperitoneally every 3 hour at various times (CT0, CT3, CT6, CT9, CT12, CT15, CT18 and CT21 (CT: circadian time); the initiation time of body-temperature elevation under a constant dark condition was set to be CT12, and 1 day was represented as CT0 to CT24), to investigate for any phase shifts.

Results and Discussion

FIG. **3** shows typical examples of a circadian rhythm phase shift when the test compounds A, B and C were administered at CT6. All of the test compounds A, B and C, which are ORL-1 receptors, showed a noticeable phase advancing action when administered at CT6 or CT9.

EXPERIMENTAL EXAMPLE 4

Antagonistic Action of the ORL-1 Receptor Antagonist on the Phase Advancement by the ORL-1 Receptor Agonist

Experimental Method and Measurement

The test compound D as an ORL-1 receptor antagonist was administered orally 1 hour before the test compound A or B was administered under the same constant dark condition as in Experimental Example 3, to investigate any phase shifts. The test compound A or B was administered intraperitoneally at CT6 when the most noticeable phase advancement was observed in Experimental Example 3.

Results and Discussion

FIG. **4** shows the results of the action of the test compound D as an ORL-1 receptor antagonist, on the phase advancement by the test compounds A and B. The phase advancement by the ORL-1 receptor agonist, any of the test compounds A and B was antagonized by pre-administration of the test compound D, as an ORL-1 receptor antagonist. Therefore, the phase advancement by the test compounds A and B was considered as a reaction via the ORL-1 receptor. In addition, it was obvious that the ORL-1 receptor antagonist showed no phase shift from the fact that no phase shift was observed for the test compound D alone.

EXPERIMENTAL EXAMPLE 5

Action of the ORL-1 Receptor Agonist on Re-Entrainment of a Light-Dark Cycle

Experimental Method and Measurement

Rats were raised for 10 days or longer with a light-dark cycle of 12 hours (illumination in a light period; 150 lux). After confirming that body-temperature is recorded to be stably changed in a day, the light-dark cycle was advanced by 6 hours by advancing the initiation time of the light period by 6 hours. By a phase response curve obtained under a constant dark condition, the test substance C was administered at the

administration time when the ORL-1 receptor agonist showed most phase advancing effect, namely, ZT6 (ZT: zeitgeber time, the initiation time of the light period was set to be ZT0, and 1 day was represented as ZT0 to ZT24), to investigate the influence on re-entrainment.

Results and Discussion

FIG. 5 shows the results of the effect of test compound C on re-entrainment after a 6-hour advancement of the light-dark cycle. The time required for re-entrainment to a new light-dark cycle was 1 week or more for the vehicle-administered group. However, the test compound C-administered group was almost re-entrained to a new light-dark cycle in about 3 days after the advancement of the light-dark cycle. In other words, the ORL-1 receptor agonist showed effectiveness for an artificially prepared jet-lag model.

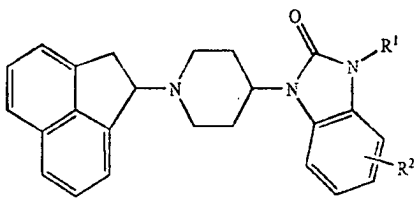
INDUSTRIAL APPLICABILITY

From the above-described pharmacological experiments, a medicament containing the ORL-1 receptor agonist, is useful for preventing and/or treating a sleep disorder, for example, a circadian rhythm sleep disorder such as jet-lag syndromes, a shift-work sleep disorder or delayed sleep phase syndromes.

This application is based on a patent application No. 2002-93398 filed in Japan, the contents of which are hereby incorporated by reference.

The invention claimed is:

1. A compound represented by the formula (I)



(I)

wherein

R^1 is lower alkyl-C(O)NR^3R^4,

R^2 is hydrogen, lower alkyl, halogen, lower alkoxy, phenoxy, benzyloxy, trifluoromethyl, nitro, amino or cyano, and

R^3 and R^4 may be the same or different, and each is hydrogen, lower alkyl or lower alkenyl, or R^3 and R^4 may bind with an adjacent nitrogen atom to form a saturated nitrogen-containing hetero ring (the hetero ring may be substituted with lower alkyl, halogen, lower alkoxy, phenoxy or benzyloxy),

a racemic mixture thereof, an enantiomer corresponding thereto or a pharmaceutically acceptable salt thereof.

2. The compound of claim 1, wherein R^2 is hydrogen, a racemic mixture thereof, an enantiomer corresponding thereto or a pharmaceutically acceptable salt thereof.

3. The compound of claim 1, wherein R^1 is lower alkyl-C(O)NR^3R^4 (either R^3or R^4 is hydrogen) or lower alkyl-C(O)NR^3R^4 wherein R^3 and R^4 bind with an adjacent nitrogen atom to form a saturated nitrogen-containing hetero ring (the hetero ring may be substituted with lower alkyl, halogen, lower alkoxy, phenoxy or benzyloxy), a racemic mixture thereof, an enantiomer corresponding thereto or a pharmaceutically acceptable salt thereof.

4. The compound of claim 1, which is

(R)-2-{3-[1-(acenaphthen-1-yl)piperidin-4-yl]-2,3-dihydro-2-oxo-benzoimidazol-1-yl}-N-methylacetamide,

a racemic mixture thereof, an enantiomer corresponding thereto or a pharmaceutically acceptable salt thereof.

5. A pharmaceutical composition comprising an effective amount of the compound of claim 1, a racemic mixture thereof, an enantiomer corresponding thereto or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

* * * * *

LEXSEE 580 F. SUPP. 2D 138

WYETH, et al., Plaintiffs, v. JON W. DUDAS, Under Secretary of Commerce for Intellectual Property and Director of U.S. Patent and Trademark Office, Defendant.

Civil Action No. 07-1492 (JR)

UNITED STATES DISTRICT COURT FOR THE DISTRICT OF COLUMBIA

580 F. Supp. 2d 138; 2008 U.S. Dist. LEXIS 76063; 88 U.S.P.Q.2D (BNA) 1538

September 30, 2008, Filed

SUBSEQUENT HISTORY: Decision reached on appeal by *Wyeth v. Kappos, 2010 U.S. App. LEXIS 300 (Fed. Cir., Jan. 7, 2010)*

COUNSEL: [**1] WYETH, Plaintiff: David O. Bickart, LEAD ATTORNEY, Patricia A. Carson, PRO HAC VICE, KAYE SCHOLER LLP, Washington, DC.

For ELAN PHARMA INTERNATIONAL LIMITED, Plaintiff: David O. Bickart, LEAD ATTORNEY, KAYE SCHOLER LLP, Washington, DC.

For JON W. DUDAS, Honorable, Under Secretary of Commerce, Defendant: Fred Elmore Haynes, LEAD ATTORNEY, U.S. ATTORNEY'S OFFICE, Washington, DC.

JUDGES: JAMES ROBERTSON, United States District Judge.

OPINION BY: JAMES ROBERTSON

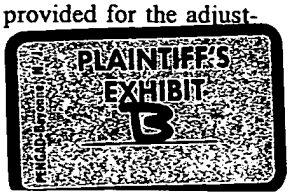
OPINION

[*139] *MEMORANDUM OPINION*

Plaintiffs here take issue with the interpretation that the United States Patent and Trademark Office (PTO) has imposed upon *35 U.S.C. § 154*, the statute that prescribes patent terms. *Section 154(a)(2)* establishes a term of 20 years from the day on which a successful patent application is first filed. Because the clock begins to run on this filing date, and not on the day the patent is actually granted, some of the effective term of a patent is consumed by the time it takes to prosecute the application. To mitigate the damage that bureaucracy can do to inventors, the statute grants extensions of patent terms for certain specified kinds of PTO delay, *35 U.S.C. § 154(b)(1)(A)*, and, regardless of the reason, whenever the patent prosecution [**2] takes more than three years. *35 U.S.C. § 154(b)(1)(B)*. Recognizing that the protection provided by these separate guarantees might overlap, Congress has forbidden double-counting: "To the extent that periods of delay attributable to grounds specified in paragraph (1) overlap, the period of any adjustment granted under this subsection shall not exceed the actual number of days the issuance of the patent was delayed." *35 U.S.C. § 154(b)(2)(A)*. Plaintiffs claim that the PTO has misconstrued or misapplied this provision, and that the PTO is denying them a portion of the term Congress has provided for the protection of their intellectual property rights.

Statutory Scheme

Until 1994, patent terms were 17 years from the date of issuance. *See 35 U.S.C. § 154 (1992)* ("Every patent shall contain . . . a grant . . . for the term of seventeen years . . . of the right to exclude others from making, using, or selling the invention throughout the United States. . . ."). In 1994, in order to comply with treaty obligations under the General Agreement on Tarriffs and Trade (GATT), the statute was amended to provide a 20-year term from the date on which the application is first filed. *See* Pub. L. No. 103-465, § 532, 108 Stat. 4809, 4984 (1994). [**3] In 1999, concerned that extended prosecution delays could deny inventors substantial portions of their effective patent terms under the new regime, Congress enacted the American Inventors Protection Act, a portion of which -- referred to as the Patent Term Guarantee Act of 1999 -- provided for the adjust-



ments that are at issue in this case. Pub. L. No. 106-113, §§ 4401-4402, 113 Stat. 1501, 1501A-557 (1999).

As currently codified, *35 U.S.C. § 154(b)* provides three guarantees of patent term, two of which are at issue here. The first is found in *subsection (b)(1)(A)*, the "[g]uarantee of prompt Patent and Trademark Office response." It provides a one-day extension of patent term for every day that issuance of a patent is delayed by a failure of the PTO to comply with various enumerated statutory deadlines: fourteen months for a first office action; four months to respond to a reply; four months to issue a patent after the fee is paid; and the like. *See 35 U.S.C. § 154(b)(1)(A)(i)-(iv)*. Periods of delay that fit under this provision are called "A delays" or "A periods." The second provision is the "[g]uarantee of no more than 3-year application pendency." Under this provision, a one-day **[**4]** term extension is granted for every day greater than three years after the filing date that it takes for the patent to issue, regardless of whether the delay is the fault of the PTO. [1] *See 35 U.S.C. § 154(b)(1)(B)*. [*140] The period that begins after the three-year window has closed is referred to as the "B delay" or the "B period". ("C delays," delays resulting from interferences, secrecy orders, and appeals, are similarly treated but were not involved in the patent applications underlying this suit.)

> 1 Certain reasons for exceeding the three-year pendency period are excluded, *see 35 U.S.C. § 154(b)(1)(B)(i)-(iii)*, as are periods attributable to the applicant's own delay. *See 35 U.S.C. § 154(b)(2)(C)*.

The extensions granted for A, B, and C delays are subject to the following limitation:

> **(A) In general.**--To the extent that periods of delay attributable to grounds specified in paragraph (1) overlap, the period of any adjustment granted under this subsection shall not exceed the actual number of days the issuance of the patent was delayed.

35 U.S.C. § 154(b)(2)(A). This provision is manifestly intended to prevent double-counting of periods of delay, but understanding that intent does not answer **[**5]** the question of what is double-counting and what is not. Proper interpretation of this proscription against windfall extensions requires an assessment of what it means for "periods of delay" to "overlap."

The PTO, pursuant to its power under *35 U.S.C. § 154(b)(3)(A)* to "prescribe regulations establishing procedures for the application for and determination of patent term adjustments," has issued final rules and an "explanation" of the rules, setting forth its authoritative construction of the double-counting provision. The rules that the PTO has promulgated essentially parrot the statutory text, *see 37 C.F.R. § 1.703(f)*, and so the real interpretive act is found in something the PTO calls its Explanation of *37 CFR 1.703(f)* and of the United States Patent and Trademark Office Interpretation of *35 U.S.C. § 154(b)(2)(A)*, which was published on June 21, 2004, at *69 Fed. Reg. 34238*. Here, the PTO "explained" that:

> the Office has consistently taken the position that if an application is entitled to an adjustment under the three-year pendency provision of *35 U.S.C. § 154(b)(1)(B), the entire period during which the application was pending before the Office* (except for periods excluded under [**6] *35 U.S.C. § 154 (b)(1)(B)(i)-(iii)*), and not just the period beginning three years after the actual filing date of the application, *is the relevant period under 35 U.S.C. § 154 (b)(1)(B) in determining whether periods of delay "overlap" under 35 U.S.C. 154(b)(2)(A).*

69 Fed. Reg. 34238 (2004) (emphasis added). In short, the PTO's view is that any administrative delay under *§ 154(b)(1)(A)* overlaps any 3-year maximum pendency delay under *§ 154(b)(1)(B)*: the applicant gets credit for "A delay" or for "B delay," whichever is larger, but never A + B.

In the plaintiffs' submission, this interpretation does not square with the language of the statute. They argue that the "A period" and "B period" overlap only if they occur on the same calendar day or days. Consider this example, proffered by plaintiff: A patent application is filed on 1/1/02. The patent issues on 1/1/08, six years later. In that six-year period are two "A periods," each one year long: (1) the 14-month deadline for first office action is 3/1/03, but the first office action does not occur until 3/1/04, one year late; (2) the 4-month deadline for patent issuance after payment of the issuance fee is 1/1/07, but the patent does not **[**7]** issue until 1/1/08, another year of delay attributable to the PTO. According to plaintiff, the "B period" begins running on 1/1/05, three years after the patent application was filed, and ends three years later, with the issuance of the patent on 1/1/08. In this [*141] example, then, the first "A period" does not overlap the "B period," because it occurs in 2003-04, not in 2005-07. The second "A period," which covers 365 of the same days covered by the "B period," does overlap. Thus, in plaintiff's submission, this patent holder is entitled to four years of adjustment (one year of

"A period" delay + three years of "B period" delay). But in the PTO's view, since "the entire period during which the application was pending before the office" is considered to be "B period" for purposes of identifying "overlap," the patent holder gets only three years of adjustment.

***Chevron* Deference**

We must first decide whether the PTO's interpretation is entitled to deference under *Chevron v. NRDC, 467 U.S. 837, 104 S. Ct. 2778, 81 L. Ed. 2d 694 (1984)*. No, the plaintiffs argue, because, under the Supreme Court's holdings in *Gonzales v. Oregon, 546 U.S. 243, 126 S. Ct. 904, 163 L. Ed. 2d 748 (2006)*, and *United States v. Mead Corp., 533 U.S. 218, 121 S. Ct. 2164, 150 L. Ed. 2d 292 (2001)*, Congress has not "delegated [**8] authority to the agency generally to make rules carrying the force of law," and in any case the interpretation at issue here was not promulgated pursuant to any such authority. *See Gonzales, 546 U.S. at 255-56, citing Mead, 533 U.S. at 226-27*. Since at least 1996, the Federal Circuit has held that the PTO is not afforded *Chevron* deference because it does not have the authority to issue substantive rules, only procedural regulations regarding the conduct of proceedings before the agency. *See Merck & Co. v. Kessler, 80 F.3d 1543, 1549-50 (Fed. Cir. 1996)*.

Here, as in *Merck*, the authority of the PTO is limited to prescribing "regulations establishing *procedures* for the application for and determination of patent term adjustments under this subsection." *35 U.S.C. § 154(b)(3)(A)* (emphasis added). Indeed, a comparison of this rulemaking authority with the authority conferred for a different purpose in the immediately preceding section of the statute makes it clear that the PTO's authority to interpret the overlap provision is quite limited. In *35 U.S.C. § 154(b)(2)(C)(iii)* the PTO is given the power to "prescribe regulations establishing the *circumstances that constitute* a failure of an applicant [**9] to engage in reasonable efforts to conclude processing or examination of an application" (emphasis added) -- that is, the power to elaborate on the meaning of a particular statutory term. No such power is granted under *§ 154(b)(3)(A)*. *Chevron* deference does not apply to the interpretation at issue here.

Statutory Construction

Chevron would not save the PTO's interpretation, however, because it cannot be reconciled with the plain text of the statute. If the statutory text is not ambiguous enough to permit the construction that the agency urges, that construction fails at *Chevron's* "step one," without regard to whether it is a reasonable attempt to reach a result that Congress might have intended. *See, e.g., MCI v. AT&T, 512 U.S. 218, 229, 114 S. Ct. 2223, 129 L. Ed. 2d 182 (1994)* ("[A]n agency's interpretation of a statute is not entitled to deference when it goes beyond the meaning that the statute can bear.").

The operative question under *35 U.S.C. § 154(b)(2)(A)* is whether "periods of delay attributable to grounds specified in paragraph (1) overlap." The only way that periods of time can "overlap" is if they occur on the same day. If an "A delay" occurs on one calendar day and a "B delay" occurs on another, they do not [**10] overlap, and *§ 154(b)(2)(A)* does not limit the extension to one day. Recognizing this, [*142] the PTO defends its interpretation as essentially running the "period of delay" under *subsection (B)* from the filing date of the patent application, such that a period of "B delay" *always overlaps* with any periods of "A delay" for the purposes of applying *§ 154(b)(2)(A)*.

The problem with the PTO's construction is that it considers the application *delayed* under *§ 154(b)(1)(B)* during the period *before it has been delayed*. That construction cannot be squared with the language of *§ 154(b)(1)(B)*, which applies "if the issue of an original patent is *delayed* due to the failure of the United States Patent and Trademark Office to issue a patent within 3 years." (Emphasis added.) "B delay" begins when the PTO has failed to issue a patent within three years, not before.

The PTO's interpretation appears to be driven by Congress's admonition that any term extension "not exceed the actual number of days the issuance of the patent was delayed," and by the PTO's view that "A delays" during the first three years of an applications' pendency inevitably lead to "B delays" in later years. Thus, as the PTO sees it, if [**11] plaintiffs' construction is adopted, one cause of delay will be counted twice: once because the PTO has failed to meet and administrative deadline, and again because that failure has pushed back the entire processing of the application into the "B period." Indeed, in the example set forth above, plaintiffs' calendar-day construction does result in a total effective patent term of 18 years under the (B) guarantee, so that -- again from the PTO's viewpoint -- the applicant is not "compensated" for the PTO's administrative delay, he is benefitted by it.

But if *subsection (B)* had been intended to guarantee a 17-year patent term and *no more*, it could easily have been written that way. It is true that the legislative context -- as distinct from the legislative history -- suggests that Congress may have intended to use *subsection (B)* to guarantee the 17-year term provided before GATT. But it chose to write a "[g]uarantee of no more than 3-year application pendency," *35 U.S.C. § 154(b)(1)(B)*, not merely a guarantee of 17 effective years of patent term, and do so using language separating that guarantee from

a different promise of prompt administration in *subsection (A)*. The PTO's efforts to **[**12]** prevent windfall extensions may be reasonable -- they may even be consistent with Congress's intent -- but its interpretation must square with Congress's words. If the outcome commanded by that text is an unintended result, the problem is for Congress to remedy, not the agency.

JAMES ROBERTSON

United States District Judge

United States Court of Appeals for the Federal Circuit

2009-1120

WYETH
and ELAN PHARMA INTERNATIONAL LIMITED,

Plaintiffs-Appellees,

v.

David J. Kappos, UNDER SECRETARY OF COMMERCE FOR INTELLECTUAL PROPERTY and DIRECTOR OF THE UNITED STATES PATENT AND TRADEMARK OFFICE,

Defendant-Appellant.

Patricia A. Carson, Kaye Scholer LLP, of New York, New York, argued for plaintiffs-appellees. With her on the brief were Richard G. Greco; and David O. Bickart, of Washington, DC. Of counsel were Thomas E. Malone, Elan Pharmaceuticals, of South San Francisco, California; and Reem F. Jishi, Wyeth, of Madison, New Jersey.

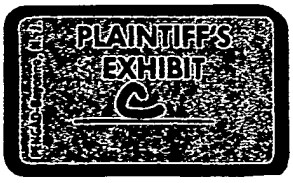
Christine N. Kohl, Attorney, Appellate Staff, Civil Division, United States Department of Justice, of Washington, DC, argued for defendant-appellant. On the brief were Tony West, Assistant Attorney General, Channing D. Phillips, Acting United States Attorney, and Scott R. McIntosh and Abby C. Wright, Attorneys. Of counsel on the brief were James A. Toupin, General Counsel, and Raymond T. Chen, Deputy General Counsel and Solicitor, United States Patent and Trademark Office, of Arlington, Virginia.

William G. James, II, Kenyon & Kenyon LLP, of Washington, DC, for amicus curiae Hospira, Inc. With him on the brief was Richard W. Ward.

Jeffrey B. Elikan, Covington & Burling LLP, of Washington, DC, for amicus curiae Pharmaceutical Research and Manufacturers of America, et al. With him on the brief were E. Edward Bruce and James P. Sullivan.

Appealed from: United States District Court for the District of Columbia

Judge James Robertson



United States Court of Appeals for the Federal Circuit

2009-1120

WYETH
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Plaintiffs-Appellees,

v.

David J. Kappos, UNDER SECRETARY OF COMMERCE FOR INTELLECTUAL PROPERTY and DIRECTOR OF THE UNITED STATES PATENT AND TRADEMARK OFFICE,

Defendant-Appellant.

Appeal from the United States District Court for the District of Columbia in case no. 07-CV-1492, Judge James Robertson.

DECIDED: January 7, 2010

Before RADER, PLAGER, and MOORE, Circuit Judges.

RADER, Circuit Judge.

I.

On summary judgment, the United States District Court for the District of Columbia held that plaintiffs Wyeth and Elan Pharma International Ltd. (collectively, "Wyeth") were entitled to extended patent term adjustments under 35 U.S.C. § 154(b) due to the Patent and Trademark Office's (the "PTO's") delay in prosecuting their patent applications. Because section 154(b) expressly permits this legal relief, this court affirms.

II.

In 1994, the law changed the effective term of a patent from seventeen years commencing from issuance to twenty years from filing. See Pub. L. No. 103-465, § 532, 108 Stat. 4809, 4984 (1994). With the change came new ways of compensating patentees for PTO-caused delays during prosecution. Under the previous seventeen-year regime, PTO-caused delays could not affect patent terms because the term commenced upon issuance after any delays during patent acquisition. Under the twenty-year term, however, those delays consumed the effective term of a patent.

In 1999, the American Inventors Protection Act amended 35 U.S.C. § 154(b) to address this new problem. The new Act promised patent applicants a full patent term adjustment for any delay during prosecution caused by the PTO. This promise took the form of three distinct "guarantees" in 35 U.S.C. § 154(b)(1):

> (A) Guarantee of prompt Patent and Trademark Office responses.--Subject to the limitations under paragraph (2), if the issue of an original patent is delayed due to the failure of the Patent and Trademark Office to [meet deadlines specified in clauses (i)-(iv)] . . .
>
> the term of the patent shall be extended 1 day for each day after the end of the period specified in clause (i), (ii), (iii), or (iv), as the case may be, until the action described in such clause is taken.
>
> (B) Guarantee of no more than 3-year application pendency.--Subject to the limitations under paragraph (2), if the issue of an original patent is delayed due to the failure of the United States Patent and Trademark Office to issue a patent within 3 years after the actual filing date of the application in the United States . . .
>
> the term of the patent shall be extended 1 day for each day after the end of that 3-year period until the patent is issued.
>
> (C) Guarantee or adjustments for delays due to interferences, secrecy orders, and appeals.--Subject to the limitations under paragraph (2) . . . the term of the patent shall be extended 1 day for each day of the pendency of the proceeding, order, or review, as the case may be.

(emphases added). To summarize, paragraph A (the "A guarantee" or "A clause") promises "prompt [PTO] responses" by extending the term of the patent one day for each day the PTO does not meet certain examination deadlines in subdivisions (i)-(iv). Id. § 154(b)(1)(A). One of these deadlines, for instance, requires a first response to a filed application within fourteen months. See id. § 154(b)(1)(A)(i). Paragraph B (the "B guarantee" or "B clause") extends the term of the patent one day for each day issuance is delayed due to the PTO's failure "to issue a patent within 3 years after the actual filing date of the application in the United States." Id. § 154(b)(1)(B). Last, paragraph C allows for adjustments relating to delays resulting from interference proceedings, secrecy orders, and appeals. Id. § 154(b)(1)(C). At issue in this case are the A and B guarantees.

Both the A and B clauses are expressly subject to paragraph 2's "In general" limitation:

> In general. To the extent that periods of delay attributable to grounds specified in paragraph (1) overlap, the period of any adjustment granted under this subsection shall not exceed the actual number of days the issuance of the patent was delayed.

Id. § 154(b)(2)(A) (emphasis added). In other words, this limitation restricts the period of adjustment when any of the "periods of delay" "overlap." This case asks this court to interpret and enforce the guarantees in the face of an "overlap" and "periods of delay" under section 154(b)(2)(A).

Section 154(b)(3) of the statute directs the PTO to "prescribe regulations establishing procedures for the application for and determination of patent term adjustments under this subsection." Id. § 154(b)(3) (emphasis added). Under the guise

of that authority, the PTO promulgated 37 C.F.R. § 1.703(f) in 2000: "To the extent that periods of adjustment attributable to the [guarantees] overlap, the period of adjustment granted under this section shall not exceed the actual number of days the issuance of the patent was delayed." (emphasis added). Other than adding the term "periods of adjustment," this language repeated the text of section 154(b)(2)(A). The regulations later defined "periods of adjustment" as "the number of days, if any, in the period beginning on the day after the date that is three years after the date on which the application was filed . . . ." 37 C.F.R. § 1.703(b) (2000). The regulation supplied no explanation about implementation or application of these rules.

In 2004, the PTO amended the regulation to replace "periods of adjustment" with "periods of delay." 69 Fed. Reg. 21706 (2004). The PTO contended that this substitution clarified the regulation:

> The language of former § 1.703(f) misled applicants into believing that [periods of A-delay] and [periods of B-delay] were overlapping only if the [period of A-delay] occurred more than three years after the actual filing date of the application. If an application is entitled to a [B-]adjustment . . . the entire period during which the application was pending before the [PTO] . . ., and not just the period beginning three years after the actual filing date of the application; is the period of delay under 35 U.S.C. 154(b)(1)(B) in determining whether periods of delay overlap under 35 U.S.C. 154(b)(2)(A).

Id. (emphasis added). Thus, the "period of delay," according to the PTO's new definition, caused the B guarantee to start with the filing of the application, not three years later. Under that interpretation, "overlap" between A adjustments and B adjustments can arise and begin during the pendency of the patent application. For example, if a patent entitled to twenty days of A adjustments issues twenty days after the three year mark, then it is only entitled to a total of twenty days of adjustment. In

other words, the entire period of A delay "overlaps" with the entire period of B delay. Using this framework, the PTO uses either the greater of the A delay or B delay to determine the appropriate adjustment but never combines the two.

Wyeth and Elan Pharma are the owners of U.S. Patent Nos. 7,179,892 (the "'892 patent") and 7,189,819 (the "'819 patent")—inventions that treat Alzheimer's disease. During the prosecution of each of their respective applications, the PTO undisputedly caused delays that gave the applicants entitlement to both A and B guarantees.

For the '892 patent, the PTO calculated 610 days of A delay and 345 days of B delay. Of the 610 days of A delay, 51 occurred more than three years after the application was filed. During the prosecution, the applicant caused 148 days of delay. Thus, under section 154(b)(2)(C), any adjustment must be reduced by that amount. See 35 U.S.C. 154(b)(2)(C). Under its greater-of-A-or-B rubric, the PTO calculated the total adjustment at 462 days—i.e., 610 (the greater of A or B) - 148 (applicant delay). According to Wyeth, however, the "period of delay" for purposes of the B clause could not have started until three years after the application's filing date. For that reason, the only possible "overlap" was any A delay occurring after the three-year mark. Because only 51 days of A delay occurred after the three year mark for the '892 patent, the adjustment, according to Wyeth, should have been 756 days—i.e., 610 (A delay) + 345 (B delay) - 51 ("overlap") - 148 (applicant delay).

For the '819 patent, the PTO calculated 336 days of A delay and 827 days of B delay. Of the 336 days of A delay, 106 occurred after the three-year mark. In this case, the applicant caused 335 days of delay. The greater-of-A-or-B rubric yields an adjustment period of 492 days—i.e., 827 (the greater of A or B) - 335 (applicant delay).

Wyeth contends the adjustment period should have been 722 days—i.e., 336 (A delay) + 827 (B delay) - 106 ("overlap") - 335 (applicant delay).

After filing petitions for reconsideration of the adjustments with the PTO, Wyeth filed the instant action in the District Court for the District of Columbia seeking an order directing the PTO to grant an adjustment per Wyeth's interpretation. Both parties filed motions for summary judgment. Citing section 154(b)(3) as evidence of a delegation of authority to draft regulations, the PTO sought Chevron deference for its interpretation. See Chevron U.S.A., Inc. v. Natural Resources Def. Council, Inc., 467 U.S. 837 (1984).

The district court sided with Wyeth, finding first that the PTO "does not have the authority to issue substantive rules, only procedural regulations regarding the conduct of proceedings before the agency." Wyeth v. Dudas, 580 F. Supp. 2d 138, 141 (D.D.C. 2008) (citing Merck & Co. v. Kessler, 80 F.3d 1543, 1549-50 (Fed. Cir. 1996)). The district court further found that even if Chevron was applicable, it would have rejected the PTO's interpretation as contrary to the plain language of the statute. As the district court put it: "The problem with the PTO's interpretation is that it considers the application delayed under [the B guarantee] during the period before it has been delayed." Id. at 142 (emphasis in original).

III.

This court reviews a grant of summary judgment without deference. Johns Hopkins Univ. v. CellPro, Inc., 152 F.3d 1342, 1353 (Fed. Cir. 1998). Summary judgment is only appropriate if the court determines that there "is no genuine issue as to any material fact and that the moving party is entitled to a judgment as a matter of law." Fed. R. Civ. P. 56(c). Because both parties in the instant case perceive no genuine

issues of material fact, this court need only decide the question of law decided by the district court. "That question is one of statutory interpretation, one that an appellate court can independently determine without deference to the trial court's interpretation." Glaxo Operations UK Limited v. Quigg, 894 F.2d. 392, 395 (Fed. Cir. 1990) (citing Madison Galleries, Ltd. v. United States, 870 F.2d 627, 629 (Fed. Cir. 1989)).

"As always, the 'starting point in every case involving construction of a statute is the language itself.'" United States v. Hohri, 482 U.S. 64, 68 (1987) (quoting Kelly v. Robinson, 479 U.S. 36, 43 (1986)). When the terms of a statute are unambiguous, "judicial inquiry is complete, except 'in rare and exceptional circumstances.'" Rubin v. United States, 449 U.S. 424, 430 (1981) (quoting TVA v. Hill, 437 U.S. 153, 187 n.33 (1978)). "Absent a clearly expressed legislative intention to the contrary, [the statute's plain] language must ordinarily be regarded as conclusive." Consumer Prod. Safety Comm'n v. GTE Sylvania, Inc., 447 U.S. 102, 108 (1980).

This court detects no ambiguity in the terms "periods of delay" and "overlap." Each term has an evident meaning within the context of section 154(b). The limitation in section 154(b) only arises when "periods of delay" resulting from violations of the three guarantees "overlap." 35 U.S.C. § 154(b)(2)(A). Significantly, the A and B guarantees expressly designate when and for what period they each respectively apply. Thus, this court can easily detect any overlap by examining the delay periods covered by the A and B guarantees.

A violation of the A guarantee—delays in meeting examination deadlines—begins with a "failure of the [PTO]" to meet one of the deadlines specified in subparagraphs (i)–(iv). Id. § 154(b)(1)(A). It ends when "the action described . . . is

taken." Id. The "period of delay" for purposes of the A clause therefore runs from the date the PTO misses the specified deadline to the date (past the deadline) of response to the underlying action.

Correspondingly, a violation of the B guarantee—the one at the heart of the issue in this case—begins when the PTO fails "to issue a patent within 3 years after the actual filing date of the application in the United States . . . ." Id. § 154(b)(1)(B). It ends when "the patent is issued." Id. The "period of delay" under the express language of the B clause therefore runs from the three-year mark after filing until the application issues.

Reading this framework into section 154(b)'s limitation provision makes it clear that no "overlap" happens unless the violations occur at the same time. Each "period of delay" has its own discrete time span whose boundaries are defined in section 154(b)(1). That is, each has a start and an end. Before the three-year mark, no "overlap" can transpire between the A delay and the B delay because the B delay has yet to begin or take any effect. If an A delay occurs on one day and a B delay occurs on a different day, those two days do not "overlap" under section 154(b)(2).

Under the PTO's strained interpretation, B delay can occur anytime after the application is filed. To the contrary, the language of section 154(b) does not even permit B delay to start running until three years after the application is filed. The PTO's position cannot be reconciled with the language of the statute. Thus, returning to the district court's decision, this time with affirming approval: "The problem with the PTO's interpretation is that it considers the application delayed under [the B guarantee] during the period before it has delayed." Wyeth, 580 F. Supp. 2d at 142 (emphasis in original).

The PTO defends its interpretation by arguing that A delays during the first three years of prosecution ultimately lead to B delays after the three-year mark from filing. Put differently, it would be double counting if A and B delays were both used to adjust because A delays "cause" B delays. In that vein, the PTO highlights various scenarios where a hypothetical patentee appears to receive some type of windfall adjustment under the statute despite being in a similar position as other applicants who receive no similar adjustment. Indeed, the statute requires as much. Nonetheless, this court perceives potential perverse results as well under the PTO's suggested interpretations. Under certain scenarios, both the PTO's interpretation and the statute itself result in some imbalanced treatment of similarly-situated patentees.

For example, the language of section 154(b) presents a slight imbalance in the following hypothetical: suppose Applicant 1 receives a patent 3 years and 30 days after filing an application. In prosecuting the application, Applicant 1 incurred 30 days of A delay before the three-year mark. In the same hypothetical situation, suppose Applicant 2 also receives a patent 3 years and 30 days after filing an application but incurred no A delay during prosecution. Notably, both patents issued the same amount of time from filing—3 years and 30 days. Nonetheless, Applicant 1 would receive a 60 day adjustment whereas Applicant 2 would only receive a 30 day adjustment meaning Applicant 1's effective term would be 30 days longer than Applicant 2.

By the same token, under the PTO's counter-statutory interpretation, suppose Applicant 1 incurs 400 days of A delay before the three-year mark with the application issuing exactly three years after filing. Suppose Applicant 2 also incurs 400 days of A delay before the three-year mark, but in addition incurs a one-year delay by the PTO

after the three-year mark. Despite the fact each applicant incurred the same A delay, under the PTO's interpretation, Applicant 1's effective term would be a full year greater than Applicant 2's effective term. Simply put, the additional B delay incurred by Applicant 2 produces a shorter effective term.

Regardless of the potential of the statute to produce slightly different consequences for applicants in similar situations, this court does not take upon itself the role of correcting all statutory inequities, even if it could. In the end, the law has put a policy in effect that this court must enforce, not criticize or correct. See Harbison v. Bell, 129 S. Ct. 1481, 1493-94 (2009) (Thomas, J. concurring) (quoting Eldred v. Ashcroft, 537 U.S. 186, 222 (2003) ("Even if the proper interpretation of a statute upholds a 'very bad policy,' it 'is not within our province to second-guess' the 'wisdom of Congress' action' by picking and choosing our preferred interpretation from among a range of potentially plausible, but likely inaccurate, interpretations of a statute.")).

The PTO also passingly refers to the second clause of section 154(b)(2)(A) for support: "the period of any adjustment granted under this subsection shall not exceed the actual number of days the issuance of the patent was delayed." 35 U.S.C. § 154(b)(2)(A). While the PTO's argument on this point is unclear, that language does not provide any support for its interpretation. Significantly, the second clause of section 154(b)(2)(A) only takes effect upon satisfaction of the first clause. See id. § 154(b)(2)(A) ("To the extent that periods of delay attributable to grounds specified in paragraph (1) overlap . . . .") (emphasis added). Viewed in this light, a "delay" must refer consistently to the violation of either the A or B guarantees. "[T]he actual number

of days the issuance of the patent was delayed" therefore refers to each day covered by a "period of delay" in the first clause with no such day counted twice.

This court has also examined the legislative history of the 1999 Act but finds nothing to rescue the PTO's cause. In the first place, only a "most extraordinary showing of contrary intentions" by Congress justifies a departure from the plain language of a statute. Garcia v. United States, 469 U.S. 70, 75 (1984). Far from intentions contrary to the meaning of section 154(b), the legislative history generally supports the interpretation required by the statutory language itself. The AIPA's section-by-section analysis states:

> Accordingly, subtitle D removes the 10-year caps from the existing provisions, adds a new provision to compensate applicants fully for USPTO-caused administrative delays, and, for good measure, includes a new provision guaranteeing diligent applicants at least a 17-year term by extending the term of any patent not granted within three years of filing. Thus, no patent applicant diligently seeking to obtain a patent will receive a term of less than the 17 years as provided under the pre-GATT standard; in fact, most will receive considerably more.

H.R. Rep. No. 106-464, at 125 (1994) (emphases added). From this, it is apparent that the statutory language should provide a minimum seventeen-year term for most patents. The outcome suggested by the language itself effectuates this goal by ensuring such a minimum term unless the applicant caused delays.

The PTO urges this court to read that passage in view of the 25-month average patent pendency at that time—that is, most patents received more than a seventeen-year term because of the shorter prosecution periods. Even taking that context into account, this court notes that the PTO's interpretation effectively creates a seventeen-year term cap where B delays are greater than A delays. In other words, any A delay before the three-year mark causes PTO delays in issuance beyond the three-year

mark—thereby violating the B guarantee. Together, these effects, under the PTO's desire to aggregate A and B delays, reduce the effective term of the patent towards seventeen years. The passage from the House report does not expressly preclude that type of effective cap, but the context suggests a very different goal of supplying adequate protection that will often be "considerably more" than the PTO's effective cap. In any event, the House report does not produce any "extraordinary showing of contrary intentions." Moreover, if the Act intended to create a seventeen-year cap, it could have easily done so with just a few words.

The PTO next highlights the belated addition of the B guarantee into section 154(b) for support. Before enactment of AIPA, section 154(b) only provided extensions for the category that now fall under C adjustments. See 35 U.S.C. § 154(b)(1)-(2) (1996). The earlier versions of AIPA added only A delays. See S. 507, 105th Cong., 143 Cong. Rec. S2678, S2696-97 (Mar. 20, 1997). Not long afterwards, B adjustments appeared in drafts of section 154(b). See H.R. 400, 105th Cong., 143 Cong. Rec. H1629, H1651 (April 17, 1997). According to the PTO, this legislative history suggests that Congress did not intend to give patentees already eligible for A adjustments additional compensation where the A delay occurred during the first three years of prosecution. Even if these ambiguous timing observations suggested some kind of substantive difference in the meaning of section 154(b), they would be wholly irrelevant to interpretation of the law itself. Such opaque timing observations hardly amount to a "most extraordinary showing of contrary intentions," especially when the language of the statute trumpets its meaning by itself. See Harbison, 129 S. Ct. at 1494 (Thomas, J., concurring) ("And Congress' silence certainly does not empower us to go even farther

and incorporate such an assumption into the text of these provisions."). In sum, legislative history—always a very dull instrument for extracting the essence of statutory meaning—provides no reason to depart from the language of section 154(b).

Last, the PTO contends that its interpretation is entitled to deference under either Chevron U.S.A., Inc. v. Natural Resources Defense Council, Inc., 467 U.S. 837 (1984) or Skidmore v. Swift & Co., 323 U.S. 134 (1944). Because the language of the statute itself controls this case and sets an unambiguous rule for overlapping extensions, this court detects no reason to afford special deference to the PTO's interpretation. See Smith v. City of Jackson, Miss., 544 U.S. 228, 267 (2005) (quoting Pub. Employees Ret. Sys. of Ohio v. Betts, 492 U.S. 158, 171 (1989)) ("Of course, it is elementary that 'no deference is due to agency interpretations at odds with the plain language of the statute itself.'").

IV.

This court therefore affirms the judgment of the district court. Section 154(b)'s language is clear, unambiguous, and intolerant of the PTO's suggested interpretation. For that reason, this court accords no deference to the PTO's greater-of-A-or-B rubric.

AFFIRMED